Volunteer melanoma screening : pros and cons

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With big enough hopes and
serious enough convictions, no
human being need die of
malignant melanoma

A Bernard Ackerman

Aan mijn ouders
Ter herinnering aan José

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PREFACE

The rise in the incidence rates of cutaneous melanoma in white populations during the last decades has caused considerable concern worldwide. Basal cell carcinomas and squamous cell carcinomas are more prevalent, however the mortality of malignant melanoma is highest of all malignancies of the skin. There were 383 deaths from cutaneous melanoma in 1992 in our country.[1]

Prognosis of malignant melanoma depends strongly on the tumour thickness. Primary surgery is the cornerstone in the treatment of melanoma. Decrease of mortality can at the moment only be reached by early recognition. Several secondary prevention programmes have been developed to manage this issue and to detect melanomas as early as possible. Screening theoretically reduces death and morbidity from cancer in general. With regard to melanoma, visual examination of the skin is an acceptable, safe, reliable, and inexpensive screening tool.

Since 1985 annual, free skin cancer/melanoma screenings sponsored by the American Academy of Dermatology (AAD) have been organized in the United States.[2,3] Also in the Netherlands such early detection campaigns have been held and developed further since 1989.[4] During all these campaigns attention was paid to all skin cancers. Because of the good prognosis and very low mortality rate of basal cell carcinomas, these tumours should not be screened for. The same, although to a lesser extent, applies to squamous cell carcinomas.

We organized a screening campaign in June 1993 in Southern Limburg, the Netherlands. In the announcements of this project special emphasis was placed on the symptoms and risk factors of melanoma and its precursor lesions. The screenings were attended by 4146 persons. Because of suspicious cancerous or precancerous lesions, 486 persons (11.7%) received a letter of referral for their general practitioner with the proposed line of management. The motivation and reasons to participate, the yield of these selective screenings, the effect of additional skin examination of persons presenting with a specific skin mark, the compliance and follow-up of positive screenees, and the awareness of the screenees of their own risk profile were subject of this thesis.

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Chapter 1

CUTANEOUS MELANOMA; GENERAL INTRODUCTION

EPIDEMIOLOGY

Cutaneous melanoma is a malignant tumour originating from the epidermal pigment cell system. These pigment cells arise from neural-crest tissue during early fetal development. They migrate to the skin and several other peripheral sites.
Melanocytes harbour in the basal layer of the epidermis and form functional units with the surrounding keratinocytes. Clusters of cutaneous pigment cells may form common naevocellular naevi, which are important precursor lesions for melanoma of the skin. Whether "melanocytes" and "naevocytes" represent different cell systems, is a matter of debate.[1,2] Their distinctive clinical behaviour and their different role in melanoma aetiology suggest a dual ontology and nosology.
Until recently, the incidence of melanoma has been rising in most western countries with a predominantly fair-skinned population. This increase can not be explained by major changes in diagnostic criteria[3]. Also in the Netherlands, with a population of 15 million, the incidence has been rising during the last few decades.[4] At the moment the incidence is approximately 13-14/100,000 inhabitants.[5] There are about 2000 new melanoma patients each year, including invasive (1700) and non-invasive (300) melanomas.
Basal cell carcinoma and squamous cell carcinoma of the skin are more prevalent than melanoma. However, the mortality from melanoma is highest of all malignancies of the skin. There were 383 deaths from cutaneous melanoma in 1992 in this country.[5] The mortality rate has been rising during the past decades, although less dramatically than the incidence rate. The rate of increase of new cases has been cited to be more rapid than for any other malignancy with exception of lung cancer in women.[6] Recent data from the United States indicate that the proportionate mortality over time changes dramatically with age.[7] The largest mortality increases are seen in the middle-aged and elderly persons. In the younger age groups mortality rates are actually decreasing. These observations underline the promise that melanoma rates may stabilize and in fact decline in the coming decades. Interestingly, in the Netherlands melanoma incidence rates have not been increasing during the period 1989-1992.[5]
Melanoma affects all age groups from adolescence. Its peak occurrence is between 40 and 50 years, with exception of acral-lentiginous melanoma and lentigo maligna melanoma. These latter types are more often seen in the elderly. Cutaneous melanoma is rarely diagnosed in childhood. When it presents in early life it often develops from a giant congenital naevus. Melanoma of childhood must not be confused with 'juvenile melanoma' (naevus of Spitz[8], spindle cell naevus). This is a benign naevocytic lesion, differing both clinically and histologically from the common

naevocellular naevus.[9] The cellular and architectural characteristics may be bizarre to give resemblance to melanoma.

In Europe the sex distribution of cutaneous melanoma is unequal. Females outnumber males to a ratio of approximately 3:2. In the United States and in Australia there is a more equal sex distribution. There is no good explanation for these differences.

In males melanoma is most often found on the back. In females the tumour is more often seen on the lower leg.

The exact cause of melanoma is unknown. Host factors as well as environmental factors seem to play a role. Especially people with a fair skin complexion, freckling traits, and tendency to burn rather than tan have an increased risk of cutaneous melanoma.[10,11] Most melanomas develop from naevocellular naevi. People with a more than average mole count have an increased risk of melanoma.[10,11] In fact, elevated numbers of naevi have been associated with the highest individual relative risks observed for melanoma.[12,13] Furthermore, a personal and/or family history of melanoma is a major risk factor.

The influence of UV radiation is still a matter of debate. Case-control and cohort studies suggest that sunlight plays an important role in the aetiology of malignant melanoma.[14] Melanoma incidence and mortality rates in North America and Australia are higher closer to the equator. The same trend does not apply to Europe with higher rates in the Scandinavian than in the Mediterranean countries. The European pattern most probably is the result of skin complexion differences. Contrarily to expectation, melanoma is mainly represented in indoor workers in the higher socioeconomic groups. This is clearly different from the occupation pattern of the nonmelanoma skin cancers, which are more common in persons with outdoor jobs. These latter tumours occur almost exclusively on sun-exposed skin. Melanomas are not concentrated on skin areas that are most exposed to the sun. These clinical and epidemiologic data led to the "intermittent exposure" hypothesis.[15,16] Especially intermittent exposure to the sun (with sunburn) of skin that is not heavily tanned or thickened, rather than regular outdoor occupational exposure seems to be of crucial importance.

However, too many inconsistencies in the evidence remain. A meta-analysis of case-control studies highlighting the links between melanoma and the sun, disclosed a weak relationship.[17] UV exposure cannot explain all epidemiologic trends. Other environmental factors must be involved. It has been suggested that water chlorination and water pollution could play an important role through recreational activities involving contact with water.[18,19] This hypothesis may also explain the increase in the relative risk for melanoma with higher socioeconomic status. In this context, UV exposure might be a confounding factor.

Human models have not really advanced our knowledge concerning the sunlight hypothesis.[20] Certain patient groups are particularly prone to develop nonmelanoma skin cancers due to exposure to harmful UV rays: patients receiving photochemotherapy (PUVA), organ transplant recipients, patients with xeroderma pigmentosum, and albino patients. Although melanomas have been reported among these categories, the incidence is very low and disproportionate to the numbers of squamous cell carcinomas that are encountered.

Artificial sources of UV radiation may play a role.[21] However, sunbed users also exhibit greater solar exposure than nonusers. Both effects are closely intertwined precluding meaningful assessment of studies on the subject.

The role of stratospheric ozone depletion is, as yet, negligible. In the years to come, even the most reasonable estimates of ozone depletion will only result in small increases in melanoma incidence, compared with the nearly doubling rate per 10 years observed in many countries over recent decades.

Finally, the immunosuppressive action of UV radiation may contribute to the induction and pathogenesis of melanoma.[22]

CLASSIFICATION

Epidemiologic, clinical and histologic data suggest that different melanoma subtypes exist. Mishima distinguished between melanomas developing from melanocytes in the basal layer of the epidermis (melanocytic melanomas) and melanomas developing from naevocellular naevi (naevocytic melanomas).[1] In this dual pathway theory the melanocyte and naevocyte are two different cell types with their own biologic features, growth characteristics and potential of malignant degeneration.

Clark et al[23] described in 1969 three clinical and histologic melanoma subtypes: superficial spreading melanoma (SSM), nodular melanoma (NM), and lentigo maligna melanoma (LMM). Later, a fourth subtype, acral-lentiginous melanoma (ALM) was added.[24]

SSM has an initial phase of predominantly horizontal, radial growth in the epidermis and papillary dermis. After a period that may last for years a vertical, invasive growth phase will follow. Especially this phase has the capacity for metastasis.

NM has a more aggressive, vertical growth phase from the beginning and it will metastasize earlier. It clinically presents often as a blue-black, dome-shaped nodule, although amelanotic forms exist. SSM and NM account for 90% of all melanomas in white populations.

Nowadays it is accepted that NM is a later stage of SSM. "Superficial" merely reflects an early microstage of melanoma and not a distinct histogenetic growth pattern. All melanomas probably pass through a stage of radial extension, but some enter the vertical growth phase more precipitously than others. It is emphasized that the histogenetic tumour type, SSM or NM, largely depends on the time the diagnosis is made.

According to Clark and co-workers[23], melanomas with radial growth phase of three rete ridges or more, should de designated as SSM; if less than three rete ridges, the tumour must be classified as NM. The cut-off point of three rete ridges seems rather artificial. The emergence of vertical growth phase bears serious reprisals upon survival. The nodular component of melanoma, whether arising in SSM or recognized "de novo" in NM, is the prognostic determinant. Yet, in Clark's terminology, the radial growth phase defines the histologic type, SSM vs NM. Thus, there is a clear discrepancy between clinicopathologic definition and biologic behaviour of these tumour types.

LMM occurs especially on sun-exposed skin in the elderly. There is no pre-existent naevus. LMM develops after a prolonged non-invasive in situ phase called lentigo maligna (Hutchinson's melanotic freckle, Dubreuihl's melanosis). Especially outdoor workers are at risk. It initially presents as a slowly growing dark brown macule with irregular borders in the face. Later, nodular invasive components arise. LMM is an entirely different entity from the other variants of melanoma because of the distinct growth characteristics.[23,25] LMM accounts for about 5 % of all melanomas. Also ALM accounts for about 5% of melanomas. It affects the palms, soles, and nail beds (subungual melanomas). This subtype is the predominant type in coloured populations. ALM appears to be more aggressive than LMM. Invasive growth will start earlier. However, it has to be taken into account that the preinvasive phase is symptomless and that patients tend to visit their doctor later for pigmented lesions on the acra than when they occur in the face.

Cellular and architectural atypia of more or less circumscribed foci of pigment cells in contiguity with the epidermis form the histopathologic hallmark of cutaneous melanoma. Early melanoma is characterized by tumour cells, isolated or in clusters, adjacent to the dermoepidermal junction. The lentiginous preinvasive component of LMM and ALM consists of isolated melanoma cells in the basal layer of the epidermis, almost in a linear pattern. In SMM and NM the tumour cells may ascend to the higher parts of the epidermis. The dominant cell type in LMM and ALM are spindle cells, in SMM and NM mostly epitheloid tumour cells are seen.

CLINICAL SIGNS AND DIFFERENTIAL DIAGNOSIS

Most melanomas arise from naevocellular naevi. Changes and symptoms in an acquired naevus are important warning signs. Some 20 years ago the ABCD(E) rule has been developed to recognize early melanoma in pigmented lesion.[26-28] This is a mnemonic for **A**symmetry, **B**order irregularity, **C**olour variegation, **D**iameter >6 mm, and **E**levation. Recently, a seven-point checklist of features of value in identifying early melanomas has been suggested.[29] These include major features: 1. changes in size, 2. changes in shape, and 3. changes in colour, and minor features: 4. diameter >6 mm, 5. inflammation, 6. oozing or bleeding, and 7. changes in sensation. Although subjective symptoms like itching, burning, or pain in a pigmented lesion might be suspicious of malignant change, most patients, especially those with early melanomas, have few changes and may have no symptoms at all. In general ulceration, bleeding and pain are late symptoms.

Dermatologists and non-dermatologist physicians see very often solitary pigmented and nonpigmented skin lesions that mimic melanoma. The most important of these will be briefly described:

Naevocellular naevus. It can be difficult to differentiate an acquired common mole from melanoma. Moles may grow and darken, especially during certain periods in life like puberty or pregnancy. More problems arise in differentiating specific precursor lesions, dysplastic or atypical naevi, from melanoma. Cutaneous melanoma and dysplastic naevi are both characterized by an irregular border, different colours and a red hue. The diameter of these lesions is usually >5 mm. Most common moles are 1-3 mm in diameter. Larger moles may give problems in differentiating them from melanoma and dysplastic naevi.

Spitz's naevus or spindle cell naevus is a benign naevocytic lesion usually occurring in children and adolescents. The clinical and histological features may give resemblance to melanoma.

Blue naevus (naevus caeruleus) is a dome-shaped, smooth, gun-metal or blue-black nodule generally less than 1 cm in diameter. It occurs on all body sites and at all ages. Malignant degeneration has been described but is uncommon.

Congenital naevi most often present as velvety, pigmented plaques. They are often covered with large terminal hairs.

Solar lentigines (lentigo senilis) are sharply defined, uniformly pigmented light brown maculas on sun-exposed sites in the elderly. Lentigo maligna is darker and shows more colour variegation. The lentigo simplex resembles lentigo senilis, but occurs on all body sites and usually at a younger age. Probably, the lentigo simplex is an early stage of seborrhoeic keratosis.

Seborrhoeic keratoses belong to the nonmelanocytic lesions. They are benign, brown or black, well-defined plaques with a "stuck on" appearance. Irritated or traumatized seborrhoeic warts can mimic melanoma.

Dermatofibromas (histiocytomas) are skin-coloured or pigmented cutaneous nodules. After pushing the surrounding skin "dimpling" can be achieved.

Pigmented basal cell carcinoma. Basal cell carcinomas principally present as pearly, translucent papules or nodules with telangiectasias. When they are pigmented it can be hard to differentiate them from melanoma.

Capillary angioma most often presents as a red vascular lesion. When it has been thrombosed it can turn dark brown or black in colour and can be easily confused with melanoma.

Pyogenic granuloma is characterized as a rapidly growing pink or red vascular nodule with a strong tendency to bleed. It can be clinically identical to amelanotic melanoma.

Kaposi's sarcoma may mimic melanoma. It presents as multiple pink, red, blue or violaceous maculas, papules, nodules, or plaques.

There are several other skin lesions which may resemble primary melanoma: subungual haematoma, black heel, Bowen's disease, strangulated skin tag, traumatized (plantar) wart, squamous cell carcinoma, and cutaneous metastases from other malignancies. The epiluminescence microscope is an easy to handle device that can be helpful in solving differential diagnostic problems.[30,31]

STAGING AND PROGNOSTIC FACTORS

The prognosis of cutaneous melanoma strongly depends on the stage of the tumour at the time of diagnosis. Staging is important to determine appropriate treatment. There are different staging systems for melanoma. Earlier methods defined three stages of melanoma: Stage I: local disease, Stage II: regional metastases, and Stage III: distant metastases. More than 90 % of all melanoma patients are diagnosed with the primary tumour alone. Consequently, the three-stage system fails to differentiate risk for mortality for the great majority of cases. Current staging systems, therefore, emphasize the role of histologic parameters by subdividing the primary tumour by level of invasion according to Clark et al[23] and lesion thickness according to Breslow.[32] Clark and co-authors correlated prognosis with increasing levels of invasion into the dermis or subcutaneous tissues. Breslow measured the vertical tumour thickness, assessed by an ocular micrometer from the top of the granular cell layer of the epidermis to the deepest point of tumour penetration. Nowadays it is accepted that the microstaging according to Breslow gives the rele-

vant prognostic information, and that Clark's level of invasion does not add substantially to this.[33] The TNM classification of the Union Internationale contre le Cancer (UICC)[34,35] and the classification of the American Joint Committee on Cancer (AJCC)[36] recommend more uniform staging systems based on the Clark and Breslow microstages.

The initial UICC staging encouraged subdivision of thickness microstages into 1 mm classes.[34] The AJCC staging proposes cutoff points at 0.75 mm, 1.50 mm, and 4 mm.[36] The current UICC system also adheres to these endpoints.[36] Conversely, the New York and Massachusetts Cooperative Group postulated natural breakpoints for tumour thickness at 0.85 mm, 1.70 mm, and 3.60 mm.[37] It is questionable whether "natural" breakpoints for melanoma thickness exist. For practical purposes it is recommended that stratification is made according to the cutoff points at 1 mm, 2 mm, and 4 mm.[33] Staging with thickness alone is very powerful and should be recommended, not at least because of its simplicity.[33]

Melanoma may form lymphogenic cutaneous metastases just around the tumour: satellites, or in the area between the primary tumour and the regional lymph nodes: in-transit metastases. Where satellites stop and in-transit secondaries begin, is a matter of convention. Currently, a 2 cm distance from the border of the primary tumour is agreed. Satellitosis heralds a poor prognosis.

Various other factors influence the course of cutaneous melanoma. Often a subdivision is made in clinical and histologic prognostic factors. A more logic and comprehensive enumeration of prognostic factors is presented in Table 1.[38] These factors involve stage and microstage of the disease, host factors, tumour characteristics, and iatrogenic factors. The stage of the disease at the time of diagnosis is probably the most important prognostic indicator. For stage I melanomas, tumour thickness according to Breslow[32] is the most important denominator. The Clark's 5-level grading system[23] is less accurate.

Cutaneous melanoma is notorious for its tendency to develop satellites and in-transit metastases. These are lymphatic deposits in the skin and subcutaneous fat surrounding the primary tumour, or within the draining area of the regional lymph nodes. Satellites and in-transit lesions carry a grave burden upon survival. Also, the presence of microscopic satellites, i.e. discrete intraspecimen tumour nests in the vicinity of the main tumour body, has a major influence on survival.[39]

The anatomic site of the tumour is of relevance with respect to prognosis. Most of the proposed concepts for anatomic stratification into high and low risk sites have

Table 1. Prognostic factors of cutaneous melanoma*

Stage of disease	Host characteristics	Tumour characteristics	Iatrogenic factors
Clinical stage	Patient's delay	Histologic type	Doctor's delay
Microstages according to Breslow and Clark	Sex	Mitotic rate	Inadequate treatment
Presence of satellites and/or in-transit metastases	Age	Vasoinvasive properties	
	Localization of tumour		
Lymph node involvement	Immunologic factors	Ulceration	
		Amelanosis	
Presence of distant metastases	Hormonal factors	Microscopic satellites	

* Modified from Rampen.[38]

been based on the classification into four major body sites: head and neck, trunk, arms, and legs. Axial locations (head and trunk) are associated with a poor prognosis compared to extremity locations. These concepts have the disadvantage of lack of controlling for other risk factors such as tumour thickness and histologic subtype. Day et al introduced the BANS concept, which identified the upper **B**ack, posterior **A**rms, posterior **N**eck, and posterior **S**calp, as independent risk areas.[40] The validity of the BANS concept has been questioned. Recently, Garbe et al were able to confirm and modify the BANS stratification by using multivariate analysis.[41] They established high risk TANS lesions: **T**horax (back and breast), upper **A**rms, **N**eck, and **S**calp.

Females have a better prognosis than males.[42] Probably there is a difference in outcome because of the location of preference of the primary melanoma. Melanomas in women are more often located on the lower leg, a site easy to see. Melanomas in men however, are more often located on the back, an anatomic region that is hard to see by the patient himself. Women present with thinner lesions and at an earlier clinical stage. Furthermore, lymph drainage is easier to predict in melanomas located on the leg than on the trunk. The exact role of sex hormones has not been elucidated yet. The possibility that oral contraceptives have an association with melanoma has never been substantiated. Pregnancy may have a deleterious effect on melanoma activity, although this suggestion was not confirmed in a recent study.[43] Prognosis in the pregnancy group in this communication was not worse after allowance for Breslow thickness. Interestingly, however, microstage was found to be unfavourable in the

pregnancy group. This may indicate exacerbation of melanoma during pregnancy, possibly because of elevated androgen levels.[44]

With regard to tumour type, it has been suggested that superficial spreading melanoma and lentigo maligna melanoma have a better outcome than nodular melanoma and acral-lentiginous melanoma. However, after correction for tumour thickness there are no differences with respect to prognosis. Other prognostic features are mitotic activity, vasoinvasive properties, and ulceration. Of these, ulceration is probably the most important risk factor.

Prompt and proper treatment is essential. Physician's delay may bear severely upon survival. The same applies to inadequate management and follow-up.

TREATMENT

Every skin lesion suspicious of melanoma should be excised. Sampling error by incisional biopsies may be a source of misinformation. Often, the type of tumour and the Breslow thickness cannot be assessed properly on a partial specimen. Furthermore, there is evidence that malignant cells could detach and reach lymphatics or blood vessels during incisional procedures, which may occasion metastatic spread.[45] Other authors have failed to detect a detrimental effect of incisional biopsy on prognosis.[46] The diagnostic excision has to be performed under field block anaesthesia with a 2-5 mm margin.

After the diagnosis melanoma has been established by histology, a therapeutic excision has to be performed as soon as possible. Because of the propensity of melanoma to develop satellites, the margin of the therapeutic excision differs from that of nonmelanoma skin cancer. The chance of development of satellites is dependant on tumour thickness.[39] Therefore, thick lesions necessitate more extensive surgery.[47] For thin melanomas with thickness $\leq$1 mm an excision margin of 1 cm is sufficient, for melanomas with thickness between 1 and 2 mm an excision margin of 2 cm is appropriate, and for melanomas with thickness >2 mm an excision margin of 3 cm is advocated.

For patients with clinical stage I disease elective or prophylactic lymph node dissection is still a matter of debate. Theoretically, there is a subgroup of patients with clinical stage I disease with microscopic metastases in nonpalpable regional lymph nodes. Prognosis could possibly be improved by early node dissection.

In general, patients with melanomas $\leq$1.5 mm thick (low risk of lymphogenic metastases) or >4 mm thick (high risk of haematogenic metastases) have little benefit from elective lymph node dissection. It has been suggested that only patients with

intermediate thickness experience better prognosis after elective lymph node dissection.[48] However, the role of elective node dissection remains a matter of many controversies since the WHO study of 1977.[49-52]

At present, studies are ongoing to show the value of sentinel node biopsy in patients with clinical stage I disease.[53,54] The aim of this procedure is to determine a subgroup of patients with microscopic metastatic disease in nonpalpable lymph nodes. Therapeutic lymph node dissection can then be performed. Theoretically, these patients would have a better prognosis. Further research is necessary to elucidate this issue.

When there are palpable lymph nodes (stage II disease), therapeutic lymph node dissection has to be performed.

In selected cases like loco-regional recurrent disease (satellites and in-transit metastases) or poor-prognosis primary lesions on the extremities, therapeutic isolation perfusion can be decided upon. Cytostatics, usually melphalan, are administered to the regional circulation in high dosages. Good results have been reported.[55] No controlled clinical trial has been performed yet comparing isolation perfusion as an adjuvant procedure with surgery alone. Studies are going on. The results of refinements of the procedure such as hyperthermic perfusion, multiple perfusions, use of cytostatic drugs other than melphalan, and combination with TNF and IFN-gamma, remain to be awaited. In the Netherlands perfusion therapy is carried out in the University Hospital Groningen, the Antoni van Leeuwenhoek Hospital Amsterdam and the Dr Daniel den Hoed Hospital Rotterdam.

There is no standardized therapy for advanced melanoma (Stage III). In general, response rates to all forms of chemotherapy are poor. DTIC (dacarbazine) is the most effective agent. Response rates vary between 10% and 40%, and remission periods are short. The subject of other modalities like radiotherapy, hormonal therapy, and immunotherapy, is beyond the scope of this review.

FOLLOW-UP

When a patient has been treated for cutaneous melanoma, close follow-up is recommended (Table 2).[47]

During each exam inspection and palpation of the area of the primary tumour has to be performed. Furthermore, palpation of the regional lymph nodes is necessary. Also, the skin between the primary lesion and the regional lymph nodes has to be examined for satellites and in-transit metastases. Inspection of the entire skin is

recommended once a year in cases with the dysplastic naevus syndrome phenotype. Routine X-rays and blood tests are not advocated. The presence of symptomless distant metastases has no inference as long as there is no appropriate systemic therapy.

Table 2. Recommended follow-up after treatment for cutaneous melanoma.

1st year	once every 2 months
2nd year	once every 3 months
3rd year	once every 4 months
4th-5th year	once every 6 months
6th-10th year	once each year

PRECURSOR LESIONS

Congenital naevi and dysplastic naevi are recognized precursor lesions to cutaneous melanoma. Congenital naevocytic naevi usually present at birth or appear soon afterwards.

About 4% of newborns have pigmented skin lesions[56]. In a minority of these cases there is a congenital naevus. Other pigmented skin lesions found at birth are mongolian spots, café-au-lait maculas, naevus of Ito, and naevus of Ota. Not all congenital naevi are present at birth; some will develop after several weeks or months after delivery.

There are different classification systems according to the size of congenital naevi. For the purpose of convenience, congenital naevi have arbitrarily been divided according to size into small congenital naevi ($\leq$1.5 cm greatest diameter), medium-sized congenital naevi (1.5-20 cm diameter), and giant congenital naevi (>20 cm diameter).[57] These sizes are based on diameter at the time of presentation. It has to be taken into account that a diameter of 6 cm is something different in a newborn infant than in an adult. Other authors prefer classification according to easy versus difficult to treat surgically.

Of all newborns 1% has a genuine congenital naevus[58]. Most of these are small congenital naevi. Giant congenital naevi are rare. They often present with multiple satellites. Congenital naevi are pigmented, sharply demarcated, and slightly elevated lesions. They often have a verrucous or pebbled surface and some terminal hair growth.

Giant congenital naevi localised in the head and neck region may be associated with leptomeningeal melanocytosis. Epilepsy, mental retardation, and leptomeningeal melanoma may occur.[59]

The risk of malignancy in congenital naevi seems to be correlated with the size of the naevus.[60] The reported incidence of melanoma in small congenital naevi is greater than what one may expect (3-20%). Rhodes and Melski[61] describe a 21-fold increased relative risk to develop a melanoma in solitary small congenital naevi. They calculated a 5% cumulative risk till the age of 60 years to develop a melanoma.

Development of a melanoma in a giant congenital naevus can occur in the first years of life.[62,63] Therefore, many authors advocate prophylactic removal of these lesions as soon as possible. Another reason to remove a giant congenital naevus are the cosmetic aspects and possible emotional effects it has on the child and parents. Theoretically, excision is the first and best choice of therapy to remove all naevus cells. This is not always possible because of the presence of naevus cells in subcutaneous tissues. Furthermore, total excision, often in multiple sessions, is not always practicable or conceivable. Split skin grafting, the use of tissue expanders, and keratinocyte cultures have their limitations. Several investigators have reported good cosmetic results from deep dermabrasion or curettage in the first few weeks of life.[64-66] This approach is based on the drop off theory. During the first few weeks the naevus cell are mainly present in the papillary dermis. Thereafter they will migrate (drop off) to deeper structures. Dermabrasion may cause a considerable reduction of the number of naevus cells. One may expect that the chance of malignant degeneration will be reduced. The cosmetic outcome of this technique is promising.

When an expectative approach is considered periodic examination of giant congenital naevi is advocated. Furthermore, patient and parents must know the early signs and symptoms of melanoma.

Because the risk of melanoma among patients with small and medium sized congenital naevi remains throughout life, prophylactic excision would be suitable. Excision performed before the age of 12 is recommended.[67]

Familial occurrence of melanoma has been known for many decades.[68] Only in 1978 Clark et al[69] and Lynch et al[70] described the familial occurrence of multiple naevi and increased risk of developing melanoma. Members of these families have the remarkable skin phenotype of multiple, atypical acquired naevi ("funny moles"). This familial syndrome was described as the B-K mole syndrome by Clark et al[69] Lynch et al described this phenomenon as the FAMMM (familial atypical multiple mole melanoma) syndrome.[70] This phenotype is now known as the dysplastic naevus syndrome (DNS).[71]

Later in 1980 dysplastic naevi were recognized not only to occur in families but also in the general population.[72] Individuals with the so-called 'sporadic' DNS have the same phenotype of multiple dysplastic naevi but without a family history of dysplastic naevi or melanomas. It is not always possible to differentiate between familial and sporadic DNS. Kraemer et al[73] proposed a DNS classification with increasing melanoma risk, according to the presence or absence of dysplastic naevi and melanomas in the patient and in first grade relatives. In the highest risk category the authors calculated a 100% lifetime risk of melanoma.
Autosomal dominant inheritance in the familial DNS has been suggested.[74] However, because of the variability of clinical expression a polygenic inheritance seems more plausible.[75]
The clinical characteristics of dysplastic naevi are:

size : >5 mm,
colour : variegate shades of brown, often with a pink-red hue,
shape : irregular, unsharp outlines,
border : fades slowly into surrounding skin,
surface : usually macular or just palpable.

Newton et al describe a scoring system of the DNS in which not only the above clinical characteristics but also the number, localisation, and distribution (especially buttocks, scalp, and iris) are of importance.[76] Dysplastic naevi differ histologically from common naevocytic naevi in their atypical architectural, cellular, and stromal features.[47]
Annual evaluation of individuals with the DNS is recommended. Detection of early melanomas developing from dysplastic naevi is the aim. Photodocumentation can be helpful. When DNS is diagnosed, examination of the first grade family members (parents, brothers, sisters, and children as from puberty onwards) is advocated.

Cutaneous melanoma has the unique character that it is a visible tumour. It has a dismal prognosis when not detected early and treated promptly and adequately. In its initial stage it has recognizable features. Thin melanomas are easy to treat by simple outpatient procedures and there is general consensus how to do.
In different countries all over the world early detection programmes have been organized for years. Prevention strategies are worth considering. The practicability and feasibility of secondary prevention by means of screening is the topic of the present thesis.

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Chapter 2

SCREENING FOR MELANOMA: METHODS, ADVANTAGES, AND LIMITS

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Incidence and mortality rates of cutaneous melanoma have been rising rapidly during the last few decades. Until recently, prediction of increased rates of melanoma in the near future were based on the belief that the incidence will continue to rise at a rate of 4% or more annually. Therefore, in recent years public health bodies and the medical profession have been contemplating and initiating educational programmes directed at primary prevention and early detection.

Currently, screening programmes for skin cancer/melanoma are increasing in number. Screening is thought to be an easy means of secondary prevention. There is the compelling intuitive appeal on the assumption that detection of early stage melanoma will be rewarding. However, screening for cancer is not always simple. This also applies to melanoma and skin cancer. Some critical features relevant to screening for skin cancer in general and melanoma in particular are reviewed here.

FUNDAMENTALS

The basic principles of screening for disease have been outlined by Wilson and Jungner.[1] These authors distinguished ten prerequisites for a worthwhile screening programme. They presented their criteria for strictly defined large-scale population screenings. However, the same criteria can also be used for selective screening exercises such as skin cancer/melanoma screening based on self-selection. The value of the Wilson and Jungner principles has been critically analyzed previously with reference to the skin cancer/melanoma setting.[2] Here we will briefly review this issue.

The condition sought should be an important health problem.

Skin cancer is very common, especially in countries with a predominantly white population. In the United States more than 500,000 new nonmelanoma skin cancers and approximately 32,000 new melanomas are diagnosed annually.[3] Melanoma is more common than cervical cancer and leukaemia.

Case fatality rates for nonmelanoma skin cancers are low. However, mortality rates are increasing.[4]

About 20% of melanoma patients will eventually die from their disease. Annual mortality from melanoma in the United States is now 6900.[3]

The rising incidence of melanoma is worrying. It is one of the principal reasons for the recent emergence of screening exercises. It is worthy of note, however, that levelling off of mortality rates with the more recent birth cohorts has been reported.[5] In the Netherlands, no increase of melanoma incidence has been observed in the period 1989-1992.[6]

There should be an accepted treatment for patients with recognized disease.

Treatment for all types of skin cancer, including melanoma, is safe, inexpensive, and effective. Management of precursor lesions such as actinic keratoses, and congenital and dysplastic naevi is more controversial.[7-9]

Facilities for diagnosis and treatment should be available.

Most types of skin cancer/melanoma can be managed by simple office procedures that are readily available. In rare instances, hospital admission or referral to a specialized centre is required. It needs emphasizing here that screening for other cancers are continuous processes; the workload generated by such campaigns is spread over the year. Screening for skin cancer/melanoma so far has involved single-occasion or once-a-year affairs with steep increases in referrals immediately after the campaigns. This may have a marked effect on workload and biopsy rate, especially in countries with a low dermatologist-to-patient ratio.[10] We found that the extra workload for the general practitioner generated by a skin cancer/melanoma screening clinic was negligible.[11]

There should be a recognizable latent or early symptomatic stage.

Melanomas and nonmelanoma skin cancers have recognizable early stages. Precursor lesions are also easily detectable.

There should be a suitable test or examination.

Screening for skin cancer means visual inspection of the skin by, preferably, a dermatologist. Visual examination of skin lesions by the dermatologist constitutes a most reliable screening tool. Koh et al[12] estimated the validity of a visual examination by dermatologists in a screening setting from 89% sensitivity for squamous cell carcinoma, to 94% for basal cell carcinoma, and 97% for melanoma. In an earlier report we found that the positive predictive value for skin cancer/melanoma in two screening campaigns was 50-60%.[13]

Few data are available on the accuracy of visual examination by dermatologists as a screening tool because of the lack of false-negative findings. Sensitivity and specificity of the screening test can only be derived from true-negative and false-negative findings. We obtained follow-up information on 1551 persons with a negative screening result; 15 persons had new skin cancers, three of which had probably been present at the original screening and had been missed.[14] The calculated sensitivity of this screening was 93.3%, its specificity was 97.8%.

The accuracy of clinical examination of the skin differs with the observer. In this respect dermatologists score distinctly better than nondermatologists.[15,16]

The test should be acceptable to the population.

A visual exam of skin lesions is painless, noninvasive, and has no side effects. Its

acceptance to screenees is high. Full-skin inspection may be embarrassing. However, sufficient data are available confirming the high acceptance of total skin examination (Table 1). This applies to patients seen in dermatologic practice as well as to persons seen during screening activities. Inconvenience and concern about privacy and modesty seem to be of trivial importance for most patients and screenees, and should not be a barrier to total skin checks.

Table 1. Patient acceptance of total skin examination

Reference	Study population	No. of persons	Acceptance
Boyce and Bernhard[36]	Office patients	182	94%
Rigel et al[30]	Screening	2239	62%
Lookingbill[37]	New office patients	1157	96%
Chiarello[38]	Office patients	1028	85%
Bolognia et al[39]	Screening	251	98%
Lee et al[40]	New office patients	874	81%
de Rooij et al[31]	Screening	1385	98%

The natural history of the condition, including development from latent to declared disease, should be adequately understood.

Early melanomas, i.e. melanomas with a predominantly radial growth phase, and favourable microstages according to Clark et al[17] and Breslow[18], have a good prognosis. These early stages may last months or even years. Melanoma can be detected far before manifestation of metastatic spread. Accurate prognostication of outcome is possible.

Precursor lesions progress to frank skin cancer very slowly. The lifetime risk of developing melanoma from atypical (dysplastic) naevi ranges from 5 to 100%, according to the personal and family histories of dysplastic naevi or melanoma.[19] The potential of malignant transformation of congenital naevi is relatively small.[20,21] Actinic keratoses evolve into invasive squamous cell carcinoma only rarely.[22] The exact value of screening for premalignant skin lesions is subject to controversy. It should be considered that screening tests and programmes indicate that although some degree of control of skin cancer and melanoma may be achieved at reasonable costs, the costs of higher degrees of control (precursor states) will be disproportionately more.

There should be an agreed policy on whom to treat.

In our view, screening must focus on melanoma only.[23] Screening concentrating on melanoma increases the rates of lesions suggestive of melanoma and dysplastic naevi, whereas the proportions of nonmelanoma skin cancers and actinic keratoses decrease. Without doubt, any type of invasive skin cancer detected through screening must be treated appropriately. Whether all precursor lesions discovered at screening should be treated or not, remains debatable. "Borderline" cases (minor actinic keratoses, vague evidence of dysplastic naevi, small congenital naevi) are preferably left untreated. Depending on definitions and criteria used, the "borderline" group may be larger than the "diseased" group, which may disproportionately burden upon the cost-effectiveness of screening.

The cost of screening, including diagnosis and treatment of positive screenees, should be economically balanced in relation to possible expenditures on medical care as a whole.

Screening for skin cancer/melanoma is inexpensive. However, the expenditures generated by the screening itself are not final costs. There are many hidden costs such as the follow-up and treatment of positive screenees, and the management of persons who do not wish to attend the screening itself but visit their own family physician or dermatologist. On the whole, however, total costs of screening for skin cancer/melanoma are regarded as relatively cheap in comparison with the costs of similar procedures for other types of cancer.

Screening should be a continuing process and not a single-occasion project.

Periodic skin checks have been advocated since 1985 by the American Academy of Dermatology on a nationwide and voluntary basis.[24] Periodic screening has the advantage of covering more and more of the population at risk. There are no useful data on the ideal frequency of skin cancer/melanoma screening.

Melanoma fulfils, for the most part, all the criteria for screening for disease enunciated by Wilson and Jungner in 1968.[1] For nonmelanoma skin cancer the fulfilment of these basic requirements is less clear.

Obvious as the integrity of the screening process for melanoma may sound, a comprehensive and scientifically respectable assessment of its value is not available. Screening has many potential benefits, but also disadvantages.[25] The benefits are clear. Some cases detected during screening will have an improved prognosis because of early intervention. Less radical treatment is necessary. This may save health-care resources. Many individuals with negative test results can be reassured and will refrain from seeking medical care. Also this may save costs. Precampaign publicity

may elicit changes in knowledge and attitude about skin cancer/melanoma in the target population, with definite primary and secondary prevention effects.
The disadvantages of screening are numerous. There is the longer morbidity of patients whose prognosis is unaltered. The resource costs may be substantial, in terms of the screening itself, the organization and manpower, and the subsequent management and evaluation of positive screenees, including those with precursor lesions and "borderline" cases. There is the dangerous fallacy of the assumption that if one is screened, all is well; absence of evidence is not evidence of absence of disease. Some persons with false-negative screen results will be given unfounded reassurance, which may occasion undue patient delays. On the other hand, those with false-positive results will be offered unnecessary surgery and, inevitably, many persons with minor or questionable disease will also be unnecessarily treated. Finally, there is the question of needless anxiety in the community in general, and in the screened population in particular.

FEASIBILITY

There are several screening procedures for skin cancer/melanoma. In the 1970s, a number of limited screenings for skin cancer were conducted in the United States at trade fairs, among farmers and rangers, or using mobile house trailers.[24] Screening programmes of a defined population have also been performed in Australia.[26] Screening at the workplace is another means of examining defined populations for skin cancer or melanoma. For example, an active diagnosis programme at the Lawrence Livermore National Laboratory was set up in response to recorded increased melanoma rates and survival after diagnosis of melanoma has been more favourable.[27] Screening of sunworshippers on beach locations has been performed in Australia[28] and the Netherlands.[29]
Annual melanoma and skin cancer screening on self-selected persons by dermatologists has been conducted in the United States since 1985.[24] This national screening programme was initiated by the American Academy of Dermatology (AAD). The effort has been received enthusiastically. Similar clinics have been held in the Netherlands.[13,23]
So far, the type of screening according to the AAD model seems to be the most feasible and ready to organize. However, screening by dermatologists is often hampered by lack of provider time. Especially in countries with a scarcity of dermatologists, like the United Kingdom, screening by dermatologists is not practicable. But also in less adverse situations, a proper and rigid type of organization

is mandatory. High numbers of attendants necessitate tight schedules in order to examine as many screenees as possible. To that end, we have tried to improve and refine our screenings.

Targeting high-risk persons should enhance the efficiency of skin-cancer screening. Melanoma has a high mortality rate as compared to nonmelanoma skin cancer. In terms of health strategy priorities, nonmelanoma skin cancers are insignificant. In our view, these cancers should not be screened for. In 1993 we organized a screening concentrating on melanoma and dysplastic naevi only.[23] The rates of lesions suggestive of melanoma and its precursors increased substantially, whereas the proportions of nonmelanoma skin cancers, actinic keratoses, and benign skin lesions decreased.

We also investigated the effect of additional complete skin examination of persons attending the screening for single lesions. Complete cutaneous examination may result in better melanoma yields than partial examination.[30] We assessed the yield of examination of the entire skin, additional to examination of intentionally shown skin lesions. We found no melanomas among 1221 evaluable cases.[31] Thus, total skin exams are probably not worthwhile. Disrobing, gowning, and chaperoning are time consuming. Many more screenees can be seen with limited provider time if only partial skin exams are performed on persons who attend for single lesions. In this way, we have been able to examine 150-200 screenees per dermatologist per day.

There should be sufficient auxiliary personnel and abundant examination rooms.[32] The dermatologist should only operate as the "screening test", rather than in a physician-to-patient role. The time allotted to each screenee must be restricted. Any set of activities, apart from the visual skin examination, should be performed by auxiliary staff.

In our view, screening clinics should not be held in private offices, in public premises, or on the beach. Screening in a hospital setting has distinct advantages. Dermatology out-patient departments are well equipped and properly lighted. Follow-up and patient compliance in the case of suspected melanoma is probably facilitated when the screening session is held at the nearby hospital.

Mass screening on the basis of population registries is impracticable. Access to screening would be inappropriate because of poor availability of the "screening test". Only dermatologists should screen. Assessment of skin images by nondermatologists is by-and-large unreliable.[15,16] This will produce relatively high rates of false-positive and false-negative screens, which will decrease the sensitivity, specificity, and predictive values of the screening exercise. Therefore, melanoma screening based on

population listings is not recommended. The medical community is not yet sufficiently prepared for embarking upon large-scale systematic and formalized screening. Melanoma screening should be regarded as an experimental procedure with attendant pros and cons. Preferably, randomized studies should be set up to evaluate its benefits.[33] However, the costs of such trial designs may be considerable.[33]

FURTHER CONSIDERATIONS

The current situation is that selective and focused screening for skin cancer/melanoma is recommended in many societies without proper evaluation of its benefits and hazards. In the absence of data on population-based screenings, we have to rely upon the results of non-randomized studies offering screening to subjects at high risk only. Interest in campaigns of selective screening is growing. Screening for melanoma only, based on self-assessment of volunteers who come forward to open-access screening opportunities, recruited by appropriate precampaign media publicity, appears rewarding. Such screenings fulfil the critical elements for an ideal secondary prevention approach as recommended by Wilson and Jungner[1], and meet the necessary practical and organizational requirements if properly planned.[2,32]

A systematic approach to the development and provision of nationwide melanoma screening programmes is a remote goal. There is the issue of disease prevalence. Screening will be more yielding in areas with a high melanoma prevalence such as Australia and the southern parts of the United States. Whether screening for melanoma is justified in areas with lower prevalence is questionable.

There is also the problem of the availability of the screening test, i.e. the dermatologist's eye. Screening is more feasible in countries with a favourable dermatologist-to-patient ratio, such as Germany. Systematic screening is virtually impossible in countries with few dermatologists, such as the United Kingdom. Screening by nondermatologists is unwarranted for the reasons already mentioned. Volunteer screening campaigns may reach only a small section of the population. If so, the impact on morbidity and mortality is low. From 1985 through 1993, over 650,000 persons were screened during the AAD skin cancer/melanoma detection programmes.[34] About 7000 presumed melanoma diagnoses were made. Assuming a predictive value of the screening test of 30-40%, the number of confirmed melanomas is only approximately 2500. In the same period, the estimated number of new melanoma cases in the United States was 248,700.[34] Thus, only 1% of all melanomas were diagnosed at the AAD screenings, which appears to be a negligible proportion. Precampaign publicity may, however, alert many people who consequently seek

medical advice beyond the open-access screenings. This secondary effect through education and health promotion can be substantial but is difficult to quantify. Public and professional educational exercises are an inherent ingredient of screening.

Ethical issues merit special attention. Skin cancer/melanoma screening should not be initiated for the benefit of the screener, but for the patient-attender only. In this context it is pertinent to mention the "borderline" problem. In our view, persons with minimal disease should not be followed. Only attendants with unequivocal malignancies or precursor lesions should be referred. The referral rate in one American study was extremely high at 31%.[12] Costs incurred to the health-care system may be considerable. The referral rate in our early studies was about 10%.[13] This discrepancy is likely to be related to the extent to which it is thought that follow-up has to be arranged for trivial or "borderline" lesions.

Programme evaluation is an essential function after implementation. Follow-up data give critical information for feedback, reinforcement, and assessment of effectiveness. Noncompliance of positive screenees is a major problem of free-of charge screenings. In Massachusetts, only 63% of positive screenees responded to repeated inquiries about recommended care.[12] Compliance with referral in our 1989-1990 campaigns was 90%.[13]

A final point relates to the cost-effectiveness of skin cancer/melanoma screening. There is the possible strain put on health services. Screening will burden the medical system with a high number of benign lesions. Many of these, however, would be removed anyhow for various reasons (irritation, bleeding, cosmetic reasons). We found an insignificant increase in the general practitioners' workload after screening exercises in Arnhem and Eindhoven.[11] On the other hand, the 1987 publicity campaign (which was not a screening campaign) in the United Kingdom was not continued in 1988 because of the disproportionate demand on health services.[35] Total costs of skin cancer/melanoma screening, including follow-up visits, hospital referrals, histopathology, etcetera, are unknown. Special surveys of economic costs to the participants and the health-care system should be mounted. We need more detailed information on hidden costs.

With regard to the efficacy of skin cancer/melanoma screening, no studies have addressed this issue satisfactorily. Crude numbers of positive screenees are inconclusive. Ideally, one would discover a high proportion of thin, good-prognosis melanomas. During our recent campaign in Southern Limburg, the Netherlands, most melanomas diagnosed were early lesions.[23] Such intermediate outcome measures, however, should be interpreted cautiously.

Everything possible most be done to enhance the present-day skin cancer/melanoma

screening exercises in the United States and elsewhere. Options for maximizing benefits, minimizing adverse effects, and lowering costs are presented here. The key components for success are the following: (1) An organizational forum for programme development, including close cooperation of epidemiologists with experience in this field, (2) An intensive precampaign public education programme, (3) dedicated personnel and suitable locations, (4) narrowing the scope of skin cancer screening by focusing on melanoma only, (5) An understanding that complete skin exams are time consuming and unproductive, (6) rigorous follow-up of positive screenees, (7) Use of overall outcome measures, such as changes in the Breslow thickness, and (8) assessment of actual and hidden costs.

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Chapter 3

FACTORS INFLUENCING PARTICIPATION AMONG MELANOMA SCREENING ATTENDERS

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Acta Derm Venereol (Stockholm); in press

SUMMARY

We surveyed the demographic profile and motives prompting to participate among people attending voluntary melanoma screening clinics in Southern Limburg, the Netherlands, in June 1993. Precampaign public announcements addressed only melanoma and its precursor lesions. All attendees completed a detailed questionnaire addressing demographic particulars and specific fixed choice questions on their motivation to attend.

There were 4146 persons attending the screening clinics. Most attendees opted for examination of a specific lesion (71%). More females than males participated. Fear of having skin cancer was an important reason to participate (27%). Of all attenders, 16% had to be convinced by relatives or friends to attend the screens, and 33% would not have visited a physician on their own initiative when there had not been a free screening. Females were more concerned about skin cancer than males. The local and regional newspapers formed the most important precampaign publicity channel.

Free melanoma screenings attract large numbers of people. Males are underrepresented. They are less aware of the risk profile of melanoma. Future screenings should target the male population.

Theoretically, morbidity and mortality from melanoma can be reduced by early detection. Public education[1,2] and selective screening[3,4] are approaches to achieve earlier diagnosis and treatment. Screening activities on melanoma and its precursors are more effective when targeting defined high-risk groups.[5]

The aim of the present study is to evaluate the demographic characteristics and motives prompting to participate among persons attending a number of selective screening clinics held in Southern Limburg, the Netherlands. The approach differed from previous attempts in the United States and other countries. So far, screening exercises have addressed all types of skin cancer, melanoma and nonmelanoma skin cancers inclusive. The Southern Limburg campaign targeted melanoma and its precursor lesions only.[5]

METHODS

In June 1993 ten voluntary melanoma screening clinics were organized in the southern part of Limburg, the Netherlands. The area counts approximately 650,000 inhabitants.

The general public was made aware of the screenings by articles in the regional newspapers, by announcements in the neighbourhood periodicals and on the local

radio and television stations, and by posters in waiting rooms of general practitioners and pharmacists, and in public libraries. Attention was focused on the risk factors and warning signs of melanoma and its precursor lesions. We especially targeted subjects with a more then average mole count, "funny looking" moles, changing moles, a fair skin complexion, a propensity to sun burn rather than tan, and a personal or family history of melanoma. No reference was made to the symptoms and signs of nonmelanoma skin cancers and their precursors.

The campaign was carried out according to the design of previous clinics conducted in the Arnhem region, the Netherlands, in 1990.[6,7] Only dermatologists and senior residents in dermatology carried out the screenings. The attenders were examined on two consecutive Saturdays at the out-patient dermatology departments of one university hospital and five district hospitals in the area. All participants received a numbered questionnaire at entry, addressing the following items: 1) sex and age, 2) place of residence, 3) level of education, 4) reason for participation: examination of a specific lesion vs complete skin check, 5) changes and symptoms of presenting skin lesions, 6) previous or intended visit to family physician for the same problem, 7) constitutional risk factors for melanoma, such as burning tendency and tanning ability, 8) publicity channels that led to participation in the project, 9) motivation for attending the screens, such as fear of skin cancer, cosmetic reasons, practical considerations, second opinion ('do not trust general physician'), interest in information on skin cancer, or other reasons (open question), 10) whether attending on own initiative or prompted by others, and 11) permission for follow-up.

In some instances more than one answer could be given. In these cases the total number of replies may outnumber the total group size. In other instances, because of missing, incomplete, or inapplicable data, the totals will not add to the total group size. Percentages were computed over the appropriate sets of information, excluding missing and inapplicable data.

Participants younger than 10 years of age did probably not fill-out the questionnaires themselves. Therefore we did also an analysis deleting this age group.

Persons with lesions regarded as suspicious of melanoma, nonmelanoma skin cancer, or distinct precursor states received a letter of referral with the presumptive diagnosis and the proposed line of management to hand over to their family physician. These persons were defined as positive screenees. No biopsies were taken during the screens. Positive screenees who had given informed consent to obtain outcome data were followed at 4 months and, in case of incomplete information, again at 10 months after the screens.

To test differences between samples the chi-squared statistic was used.

RESULTS

In total, 4146 persons (60% females and 40% males) attended the screenings. Among these, 55 melanomas and 17 lentigo malignas were found clinically.[5] The majority of participants were between 20 and 49 years of age (52%). The female to male ratio was highest in the age category 20-39 years.

Seventy-one percent of the screenees intended to show a specific skin lesion they were worried about. A general skin check was opted for by 23%, whereas 6% gave both reasons for their visit (specific skin mark plus total skin check). Females opted more often for examination of a specific skin mark than males. In Table 1 the most important reasons for participation are summarized according to gender.

Table 1. Gender differences regarding factors influencing participation

Reason or motivation to participate	Males	Females
Specific skin lesion (vs general skin check)	71%	78% ***
Signs or symptoms of cutaneous lesions	45%	58% ***
Prompted by relative or friend (vs attending on own initiative)	22%	12% ***
Fear of skin cancer	23%	29% ***
Cosmetic reasons	19%	23% **
Practical considerations ("Saturday is day off")	27%	19% ***
Second opinion ("Do not trust general physician")	5%	7% *
Interest in information on skin cancer	24%	29% ***

Significant levels: *** $p<0.001$; ** $p<0.01$; * $p<0.05$.

Among the persons attending with specific skin lesions, 58% had noticed changes in these lesions, whereas among those who attended for a general skin check, only 36% indicated changes in some skin lesions ($p<0.001$). Women indicated signs or

symptoms more frequently than men. In 60% of the screenees, these changes had been present for over 1 year. Delays of more than 1 year were as frequent in males as in females. Elderly persons exhibited substantially longer delays before attending the screening opportunity than persons of younger age ($p<0.001$).

Thirty-six patients of the screenees had consulted their family physician or dermatologist previously for the same reason. Females scored higher in this respect than males (39% vs 32%; $p<0.001$).

Of all screenees, 33% would not have visited a physician on their own initiative for the same problem when there had not been a screening campaign; 32% doubted whether they would have consulted a physician, and 36% stated that they would have scheduled a consultation in the near future anyhow. Females indicated more often than males that they would have consulted a physician for their lesion(s) anyhow, even when there had not been a screening campaign (38% vs 29%; $p<0.001$). Of the participants with symptoms, 22% stated that they probably would not have visited their physician when there had not been a free screening.

Of all participants, 16% had to be prompted by relatives or friends to attend the screens. Considerably more males than females were persuaded by others to attend. Especially, persons without any signs or symptoms more often attended in response to urging from other people than those with signs or symptoms (20% vs 13%; $p<0.001$).

Fear of having skin cancer was an important reason to attend the screenings in 27% of the participants. Females were more concerned of having skin cancer than males. Fear of skin cancer was more evident in those with a low education level as compared with screenees with higher education ($p<0.001$). Also, fear of skin cancer was more frequently recorded by elderly persons than among the younger age groups ($p<0.001$). The presence of signs and symptoms of skin lesions, as compared with their absence, was more frequently associated with fear of skin cancer (32% vs 21%; $p<0.001$).

An equally important reason for participation was the interest in information about skin cancer (27%). The interest in information was highest in females (Table 1). Less important factors influencing participation were cosmetic or practical reasons (respectively 21% and 22%), and obtaining a "second opinion" from the screening dermatologist (6%). Twenty percent of the participants stated under "other reasons" that they visited the screenings "to have a skin check by a dermatologist".

The regional newspapers and neighbourhood magazines played the most important role in the precampaign awareness programme; 76% reported being informed about the campaign through these newspapers or periodicals. There was a striking difference in information through the newspapers and magazines with regard to

level of education and age of the participants. Persons with a low education level got the information more frequently from newspapers and magazines than attendees with a higher education level ($p<0.001$). Likewise, elderly persons were more often informed through the newspapers and magazines than younger persons ($p<0.001$). Less important channels of information were relatives or friends (20%), and posters (15%). Gender differences in the responses to various types of advertisements were only conspicuous regarding the information through posters.
The announcements on the local radio and television station were reported by respectively 2% and 5% of the screenees only.
When the age group till 10 years was discarded, the overall results were not affected.
Assessment of the reasons for attending among the confirmed melanoma cases ($n=13$) was considered meaningless because of the small group sizes.

DISCUSSION

The demographic profile of the selective melanoma screening clinics in Southern Limburg shows a preponderance of female attendees over males (3:2). The melanoma population in the Netherlands is characterized by relatively more female than male patients, also at the ratio of about 3:2.[8] This may suggest that the precampaign publicity attracted a screening population that is compatible with the reported gender distribution of melanoma patients. However, screening for skin cancer and melanoma in various parts of the world consistently demonstrates a preponderance of females, even in areas with a more equal melanoma distribution among the sexes.[6,9-12] Therefore, it is likely that the female preponderance noticed in this series a characteristic of screening in general.
Male patients seem to be less aware of malignant melanoma.[13,14] They attend their general physician or dermatologist with more advanced disease compared to females.[15-17] Especially males should theoretically take advantage of early detection by public campaigns and screening exercises. It is therefore advisable to give special emphasis in such campaigns to reach the male population.[18]
In order to answer the question to what extent selective screening has an additional value above the existing health care system, it is important to investigate subjects who would not have visited their general practitioner for the same problem when there had not been organized a screening. In the present study particularly males would not have visited their general physician for the same problem. The same event has been reported by Girasek.[19]
There were 641 individuals who were prompted to attend by others (16%). Again,

males were more often persuaded by relatives or friends than females. In the study of Koh et al only 7% of all attendees were convinced by others to attend the screens.[12] Also in his study more males than females had to be prompted by others (10% and 6%, respectively). These observations have certainly to do with the fact that males are less interested in their naevi[20] and are less aware of early signs and symptoms of melanoma.[14] Koh et al showed that males in particular failed to recognize their own melanoma.[13] Even lesions at "easy to see areas" were less often self-discovered.

The local and regional newspapers played an important role in the promotion of our screenings. In 76% of the screenees the written media were the most relevant publicity channel. We only used the local and regional press to launch our programme. These papers are mainly read by persons of the lower social strata. A national screening campaign, with announcements in the national newspapers, would undoubtedly attract more people of a higher education level. Posters distributed in waiting rooms of general physicians and pharmacists, and in public libraries appeared to be of minor importance. They were most often noticed by females. Posters might play a more important role if they are distributed at different places such as sporting facilities, banks, etcetera. The local radio and television were of negligible importance in this study. During screenings in the United States television has generated substantially more impact on the precampaign awareness programme.[12,19] Expectedly, the role of television will increase when the national stations are used.

It has to be taken into account that information obtained by this questionnaire only reflects the motivation and reasons to participate of those who did visit the screenings. Koh et al[12] showed that (self-selected) participants of skin cancer and melanoma screenings differ from the general population in their risk profile and that they seem to be at appropriately high risk. Furthermore, the yields of confirmed skin cancers of these screenings are relatively high as compared with the expected harvest of prevalent cases from the general population.[6,11,21,22] This selective attendance is of importance with regard to costs and effectiveness.

In the precampaign awareness programme of the present study special attention was paid to the signs and risk factors of melanoma. The question arises whether there are other groups among the general population who are at a more than average risk, not because of clinical characteristics or phenotypic risk profile but because of their minimal awareness of melanoma. Results from studies from Newman et al[23] and Melia et al[14] indicate that awareness is lowest among men, low socio-economic groups, the under 25s, the elderly, and those without a partner. Males visit screening opportunities more often after prompting by spouses, relatives, or friends. Such persons may play an important role in the early recognition of

melanoma. It is known that melanoma is diagnosed at an earlier stage in married persons.[13,24]

Melanoma screening as presented in this communication is feasible, seems to fulfil a need. The selection of screenees at more than average risk might be improved further. Motivation among the general public and disease perception are important issues that need special emphasis.

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Chapter 4

SKIN CANCER SCREENING FOCUSING ON MELANOMA YIELDS MORE SELECTIVE ATTENDANCE

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SUMMARY

Background: Screening theoretically reduces death and morbidity from malignant melanoma. The rationale of screening for nonmelanoma skin cancer is more debatable, since mortality rates are very low.

Methods: We organized a screening campaign in Southern Limburg, the Netherlands in 1993. Press releases and public announcements referred only to melanoma. The results were compared with similar campaigns in Arnhem and Eindhoven, the Netherlands, in 1990; these, however, addressed skin cancer in general.

Results: There were 4146 people attending the 1993 screenings, compared with 2463 in 1990. The proportion of screenees with lesions suggestive of melanoma increased from 1.1% in 1990 to 1.7% during the 1993 campaign ($p=0.04$). The proportion of dysplastic naevi rose from 2.1% to 7.7% ($p<0.001$). Nonmelanoma skin cancers were less often encountered (3.7% in 1990 vs 2.6% in 1993; $p=0.009$). Actinic keratoses were also less numerous (6.3% vs 1.5%; $p<0.001$).

Conclusion: Screening concentrating on melanoma increases the rates of lesions suggestive of melanoma and dysplastic naevi, whereas the proportions of basal and squamous cell carcinomas, and actinic keratoses decrease. These findings may have important implications with regard to the cost-effectiveness of skin cancer screening efforts.

Prognosis of malignant melanoma depends strongly on early recognition. Screening as a means of secondary prevention enhances early detection and, theoretically, reduces death and morbidity from melanoma.[1,2] Visual examination of the skin by dermatologists is an acceptable, reliable, and inexpensive screening tool. Since 1985 voluntary skin cancer and melanoma screening clinics have been held in the United States.[3-7] Similar clinics were organized in the Netherlands in 1989 (Oss) and in 1990 (Arnhem and Eindhoven).[8-10] The screening exercises in the Netherlands were pilot studies to investigate the practical implications of such screenings. All screenings in the United States and the Netherlands so far have concentrated on skin cancer in general, including both melanoma and nonmelanoma skin cancer.

Mortality from nonmelanoma skin cancer is low. In terms of health strategy priorities, these skin lesions are insignificant. One may argue that skin cancer screening should be confined to malignant melanoma. We studied the proportions of melanomas, dysplastic naevi, and other pigmented skin lesions and nonmelanoma skin cancers, after a screening programme with media attention focusing on melanoma only.

MATERIALS AND METHODS

In June 1993, free melanoma detection clinics were conducted in Southern Limburg, the Netherlands, under the auspices of the Dutch Academy of Dermatology and Venereology and the Comprehensive Cancer Centres IKL (Maastricht, the Netherlands) and IKO (Nijmegen, the Netherlands). The area encompasses approximately 650,000 inhabitants. All dermatologists in the region participated in the study. The screenees were examined at six hospital locations on a first come, first served basis. The programme was announced in the regional newspapers, on the regional radio and television stations, and by posters in waiting rooms of general practitioners and in pharmacies and public libraries. Special emphasis was placed on the risk factors and symptoms of early malignant melanoma and its precursor lesions. No reference was made to the nonmelanoma skin cancers and their risk denominators.

Because of the large turnout, skin examinations were confined to specific lesions the attendants were worried about. Systematic examination of the entire skin was performed only on those who intentionally opted for a complete skin check and on those who showed a special skin mark that was suggestive of dysplastic naevus or melanoma. These factors were the same ones used in the 1990 programmes.

When more than one clinical diagnosis was considered, only the single worst diagnosis was recorded. No biopsies or therapeutic interventions were performed during the screenings.

The participant received a letter of referral with the proposed line of management to his or her family physician when a cancerous or precancerous lesion was suspected. Persons with borderline lesions or minimal extent of precursor states were not referred so as to avoid undue concern and medical treatment. Four months after the campaign, persons with a positive screen result were contacted for follow-up. Those who did not respond were approached again after 10 months.

The results of the Southern Limburg campaign were compared with those of two earlier campaigns in Arnhem in June 1990 and in Eindhoven in October 1990. The screenings in Arnhem and Eindhoven had been planned and executed in a similar way, but the precampaign public releases had emphasized skin cancer in general instead of melanoma in particular. To test for differences between the two populations, the chi-squared statistic was used.

RESULTS

In Arnhem and Eindhoven in 1990, a total of 2463 participants had been registered. The campaign in Southern Limburg in 1993 attracted 4146 participants. There was no marked difference in the sex ratio between the 1990 and 1993 exercises. In Arnhem and Eindhoven, 47% of the screenees were younger than 50 years, compared with 66% in Southern Limburg. The shift toward younger participants was highly significant ($p<0.001$). Table 1 summarizes the demographic profile of the attendees to both campaigns.

Table 1. Demographic profile of attendees at the screening clinics in 1990 and 1993

	1990* (n=2463)	1993# (n=4146)	p
Sex distribution			
M	966 (39.4%)	1678 (40.5%)	
F	1484 (60.6%)	2465 (59.5%)	>0.05
Data missing	13	3	
Age distribution			
≤19 yrs	195 (7.9%)	588 (14.3%)	
20-29 yrs	223 (9.1%)	695 (16.9%)	
30-39 yrs	315 (12.8%)	698 (16.9%)	
40-49 yrs	417 (16.9%)	747 (18.1%)	
50-59 yrs	491 (20.0%)	593 (14.4%)	
60-69 yrs	518 (21.0%)	539 (13.1%)	
≥ 70 yrs	302 (12.3%)	262 (6.4%)	<0.001
Data missing	2	24	

* Arnhem and Eindhoven, the Netherlands
\# Southern Limburg, the Netherlands.

Table 2 shows the most relevant findings related to skin malignant neoplasms. The proportion of screenees with lesions clinically suggestive of melanoma was higher in 1993 than during the campaigns in Arnhem and Eindhoven. Together, melanoma and lentigo maligna were suspected in 1.7% of the screenees in 1993, compared with only in 1.1% in 1990 ($p=0.04$). Lesions suggestive of nonmelanoma skin cancer were less numerous in 1993. The proportion of persons with presumptive nonmelanoma skin cancer (basal and squamous cell carcinoma and Bowen's disease) decreased from 3.7% in 1990 to 2.6% in 1993 ($p=0.009$).

Table 2. Presumptive diagnoses of melanoma and nonmelanoma skin cancer

	1990* (n=2463)	1993# (n=4146)	p
Melanomas			
Malignant melanoma	21	55	
Lentigo maligna	5	17	
Total$	26/26 (1.1%)	72/69 (1.7%)	0.04
Nonmelanoma skin cancers			
Basal cell carcinoma	84	95	
Squamous cell carcinoma	5	6	
Bowen's disease	3	13	
Total$	92/91 (3.7%)	114/106 (2.6%)	0.009

* Arnhem and Eindhoven, the Netherlands
\# Southern Limburg, the Netherlands
$ Numbers of malignant neoplasms/numbers of attendees; percentages and p values relate to numbers of attendees.

Table 3. Presumptive diagnoses of precursor lesions and benign conditions

	1990* (n=1817)	1993# (n=4146)	p
Naevi			
Naevocellular	724 (39.9%)	2333 (56.3%)	<0.001
Dysplastic	38 (2.1%)	319 (7.7%)	<0.001
Congenital	52 (2.9%)	370 (8.9%)	<0.001
Halo	10 (0.6%)	43 (1.0%)	>0.05
Blue	9 (0.5%)	24 (0.6%)	>0.05
Lentigines, freckles	120 (6.6%)	229 (5.5%)	>0.05
Keratoses			
Actinic	114 (6.3%)	63 (1.5%)	<0.001
Seborrhoeic	600 (33.0%)	1118 (27.0%)	<0.001
Dermatofibromas	134 (7.4%)	194 (4.7%)	<0.001
Vascular lesions	114 (6.3%)	124 (3.0%)	<0.001
Fibromas, skin tags	89 (4.9%)	168 (4.1%)	>0.05
Cysts	62 (3.4%)	27 (0.7%)	<0.001
Viral warts	43 (2.4%)	39 (0.9%)	<0.001
Eczema, psoriasis, fungal infections	182 (10.0%)	115 (2.8%)	<0.001

*Arnhem and Eindhoven, the Netherlands
#Southern Limburg, the Netherlands.

Data pertaining to precursor lesions and benign skin conditions are presented in Table 3. At two of six clinics in the Arnhem region, no presumed diagnoses had been recorded, apart from skin malignant neoplasms. The total number of attendees with evaluable data for precursor lesions and benign skin marks in 1990 was 1817. The proportion of dysplastic naevi had increased substantially in 1993 as compared with 1990. Also, common and congenital naevocytic naevi were more frequently encountered in 1993. However, the proportion of freckles and solar lentigines had slightly decreased. Actinic keratoses were distinctly more numerous in 1990 than in 1993. Finally, clinically benign lesions and generalized skin conditions, such as seborrhoeic keratoses, dermatofibromas, angiomas, viral warts, eczema, psoriasis, and fungal infections, were less often seen during the last screening, all at a statistically significant level.

Follow-up of the persons with presumed skin malignant neoplasms seen in 1990 was only achieved in the region of Arnhem, with 1961 participants; no follow-up data were available for the clinic held in Eindhoven with 502 screenees. In 1993, follow-up was accomplished at all clinics in Southern Limburg. The proportion of melanomas confirmed by pathologic examination was similar in both groups (0.3%). Six melanomas were diagnosed in Arnhem and 13 in Southern Limburg.

Table 4. Numbers of malignant neoplasms confirmed by pathologic examination

	1990* (n=1961)	1993# (n=4146)	p
Melanomas			
Lentigo maligna	1	4	
Melanoma in situ	0	3	
Invasive melanomas			
<1 mm thick	1	5	
≥ 1 mm thick	3	1	
thickness unknown	1	0	
Total$	6/6 (0.3%)	13/13 (0.3%)	0.04**
Nonmelanoma skin cancers			
Basal cell carcinoma	40	43	
Squamous cell carcinoma	1	0	
Bowen's disease	4	1	
Total$	45/41 (2.1%)	44/42 (1.0%)	0.001

* Arnhem, the Netherlands # Southern Limburg, the Netherlands

$ Numbers of malignant neoplasms/numbers of attendees; percentages and p values for nonmelanoma skin cancers relate to numbers of attendees

** Mann-Whitney U test, considering lesion thickness.

Most melanomas diagnosed in Southern Limburg were early lesions: only one patient had a melanoma 1 mm thick or more. In Arnhem, tumour microstage was documented in five of six cases; three of these were 1 mm thick or more. This shift to thinner lesions was statistically significant (p=0.04, Mann-Whitney test). The proportion of screenees with nonmelanoma skin cancer confirmed by pathologic examination was larger in Arnhem than in Southern Limburg (2.1% and 1.0%, respectively; p=0.001). Table 4 gives an overview of the malignant neoplasms confirmed by pathologic examination at follow-up.

The difference in age distribution of both study populations prompted us to perform a logistic regression analysis, including sex and age in the model. For all naevocellular lesions: (common naevi, congenital naevi, dysplastic naevi, and melanoma), the odds ratios were statistically significantly increased in the Southern Limburg screening as compared with the Arnhem screening. The odds ratio for melanoma, including lentigo maligna, was 1.84 (95% confidence interval, 1.16 to 2.92).

COMMENT

Screening offers much potential for reducing mortality from malignant melanoma. However, many questions about proper methods of screening for skin cancer and melanoma and its ultimate value remain unanswered.[1,2,11-13] Detection campaigns have definite unwarranted effects in terms of creating anxiety and incurring extra health expenditures. Since 1985, the American Academy of Dermatology has been sponsoring open-access screening clinics.[3-7] Similar clinics have been organized in the Netherlands.[8-10] So far, attention has been paid to both melanoma and nonmelanoma skin cancer. Nonmelanoma skin cancer is seldom lethal and does not warrant screening. Screening confined to melanoma instead of screening for skin cancer in general may considerably increase the yield of positive screens.

This study shows that when special emphasis is placed on the risk factors and symptoms of malignant melanoma and its precursor lesions in the public announcements and press releases, the percentages of screenees attending with skin lesions clinically suggestive of common moles, congenital naevi, dysplastic naevi, and melanoma are higher. However, skin lesions clinically suggestive of squamous cell carcinoma, basal cell carcinoma, and actinic keratoses are less frequent. This also applies to benign skin conditions, eg, eczema, psoriasis, dermatofibromas, and seborrhoeic keratoses.

We also compared the biopsy-proved skin malignant neoplasms between both campaigns. Six melanomas were recorded in 1990: one lentigo maligna and five

invasive melanomas. In the 1993 campaign, 13 melanomas were diagnosed: four lentigo maligna lesions, three in situ superficial spreading melanomas, five invasive melanomas less than 1 mm thick, and only one thick melanoma (2.1 mm). Although the proportion of confirmed melanomas in both programmes was similar (0.3%), the relative yield of early lesions was distinctly higher in the 1993 programme ($p=0.04$). The total number of confirmed melanomas might have been higher in Southern Limburg if all suspected melanoma cases had been followed up. Follow-up was incomplete for two possible melanomas and two cases of lentigo maligna. In Arnhem all presumptive melanoma diagnoses were followed up. The total of 13 confirmed melanomas seems rather low. There were 72 potential melanomas diagnosed, including 17 lentigo malignas, in 69 persons. Sixty-eight tumours were adequately followed up. This gives a positive predictive value of only 19%. This low test performance probably results from the inclusion of many pigmented lesions with low clinical suspicion among the presumptive melanoma diagnoses.

The yield of histologically confirmed dysplastic naevi was 48. In Arnhem only 10 dysplastic naevi were histopathologically confirmed. Despite the incomplete follow-up of persons with presumed dysplastic naevi in both screening exercises, and the rather subjective interpretation of diagnostic minutiae of dysplastic naevi by individual dermatologists and histopathologists, we are confident that the true rate of dysplastic naevi was substantially higher in the recent campaign.

The peak occurrence of cutaneous melanoma is at 40 to 50 years of age. Nonmelanoma skin cancer generally afflicts the elderly. Our 1990 campaigns exhibited a relative excess of elderly persons with peak attendance rates between 40 and 70 years. The 1993 series showed a preponderance of adult screenees, with peak attendance rates between 20 and 50 years. The shift toward a younger cohort is encouraging. In this respect, age is probably not a confounder. Nevertheless, we executed a multivariate analysis, which disclosed screening location to be an independent risk variable. In Southern Limburg, significantly more melanomas were clinically diagnosed than in Arnhem.

Attendees of skin cancer and melanoma screening programmes differ from the general population in their risk profile.[14] People attending in response to the multimedia publicity efforts seem to be at appropriately high risk. Screening exercises show a relatively high yield of confirmed skin cancers, as compared with the expected harvest of prevalent cases from the general population.[3,6,7,9] On the other hand, the proper value of self-examination and self-selection as a screening tool has been questioned.[15] To maximize the yield of screening, it is imperative to tailor programmes to attract

those persons at highest risk. Our survey demonstrates that precampaign publicity messages must focus on melanoma.

A most promising finding of our project is the decreased proportion of nonmelanoma skin cancers and certain precancerous states of low or negligible clinical and epidemiologic concern: basal and squamous cell carcinomas, and actinic keratoses. It is questionable whether screening procedures can alter the natural course of nonmelanoma skin cancer in a significant proportion of those screened. One of the major drawbacks of the rather unfocused screening efforts on skin cancer conducted so far in the United States and in the Netherlands is the initiation of insignificant and borderline cases into the medical circuit. Screening only for melanoma may provide a means of increasing the detection rate of an important and potentially lethal disease. Selective screening for melanoma may improve cost-effectiveness. It also may decrease the risk of overtreatment of a great number of persons with minor or questionable disease.

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Chapter 5

TOTAL SKIN EXAMINATION DURING SCREENING FOR MALIGNANT MELANOMA DOES NOT INCREASE THE DETECTION RATE

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SUMMARY

Total skin examination during public screening for malignant melanoma is often advocated, but the benefit of this approach has not been established properly. We assessed the yield of examination of the entire skin, in addition to examination of intentionally shown skin lesions, in people attending melanoma screening clinics in Southern Limburg, the Netherlands, in 1993. Of the 4146 attenders, 2910 (70%) showed a specific skin spot. Additional examination of the entire skin was offered to 1385 people. There were 1221 evaluable cases. Fourteen presumptive diagnoses of malignancies were encountered: seven malignant melanomas, all with low clinical suspicion, and seven basal cell carcinomas. Histology revealed three basal cell carcinomas. No malignant melanomas were confirmed by histology. It is concluded that additional total skin examination during screening for malignant melanoma is not worthwhile, except perhaps for persons presenting lesions that are suspicious of melanoma or dysplastic naevi.

Screening for malignant melanoma aims at timely recognition and, thus, theoretically reduces death from this tumour. Several questions about proper screening methods remain unanswered.[1-3] One problem is the value of inspection of the entire skin in screenees who intend to show only one specific skin spot. Most authors advocate additional, total, skin examination.[1,4] Complete skin examination seems to have certain advantages, as most malignant melanomas are found on covered parts of the body. On the other hand, an entire skin examination is time consuming, and may be embarrassing. The aim of this study was to investigate the yield of additional total skin examination in participants of a melanoma screening campaign.

MATERIALS AND METHODS

In June 1993, a number of voluntary melanoma screenings were conducted in Southern Limburg, the Netherlands.[5] Participants were asked to indicate whether they opted for examination of one, or a few, specific skin mark(s), or for a complete skin check. Those who intended to show a specific lesion were offered additional, total skin examination, when time and staffing allowed.

All those showing a skin lesion suggestive of malignant melanoma or dysplastic naevus were formally offered a total skin check, according to the study protocol. These screenees were excluded from the final analysis of additional total skin examinations. If a malignancy or premalignancy was suspected, the participant received a letter of referral with the proposed line of management to his/her general practitioner. All

positive screenees were followed. Four months after the campaign, treatment particulars and histopathology data were compiled. With regard to the non-responders, follow-up was repeated after 10 months.
When appropriate, the chi-squared statistic was used to test for differences between two samples. When the sample sizes were too small for a chi-squared test, Fisher's exact probability test was used.

RESULTS

A total of 4146 participants were screened. Of these, 2910 (70%) opted for examination of a specific skin mark, and 1197 (29%) for a complete skin check (39 unknown). Of the 2910 persons who intended to show a specific skin lesion, 1385 (48%) were offered additional total skin examination. Of these, 1356 (98%) agreed to examination of the entire skin. Of the 1356 screenees who accepted an additional skin check, 135 showed, at first examination, a skin mark clinically suspicious of dysplastic naevus or malignant melanoma. These persons systematically underwent a total skin check, according to the study protocol. Thus, 1221 screenees remained for evaluation.

Table 1. Yield of additional complete skin examination (n=1221)

Clinical diagnosis	Number of cases	Histopathological diagnosis
Malignant melanoma	7	1 Dysplastic naevus
		3 Common mole
		2 Trauma
		1 Lentigo simplex
Basal cell carcinoma	7	3 Basal cell carcinoma
		1 Seborrhoeic wart
		1 Naevocellular naevus
		1 Treatment without histology
		1 Incomplete follow up

There were 14 presumptive diagnoses of malignancies, seven of malignant melanomas, with a low clinical suspicion, and seven of basal cell carcinomas (Table 1). Follow-up was complete in 12 instances (86%). One person, with a presumed basal cell carcinoma did not visit her physician, although she was encouraged to do so twice. One screenee, with a presumed basal cell carcinoma, was treated without histology. Histology in the compliant cases revealed three basal cell carcinomas. No biopsy-proved melanomas were encountered.

Of the 49 screenees with presumptive diagnoses of premalignancies seen on additional total skin examination, follow-up was achieved in 45 cases (92%). No malignancies were detected on histology in this group.

The initial examination of lesions about which the attendants were concerned, including cutaneous examination in those who opted initially for a total skin check, yielded substantially more presumptive malignancies and premalignancies than the additional total skin examination (Table 2). Histology revealed 13 malignant melanomas (in 13 persons) and 44 nonmelanoma skin cancers (in 42 persons) following initial screening. These findings contrast with no melanomas at all ($p=0.05$), and only three basal cell carcinomas ($p=0.007$), respectively, detected in the additional, total skin examination group.

Table 2. Numbers of presumptive malignancies and premalignancies detected at primary examination and during additional total skin examination

Clinical diagnosis	Initial examination n=4146	Additional total skin examination n=1221	Significance (p)
Malignant melanoma*	69 (1.7%)	7 (0.6%)	0.005
Basal cell carcinoma	95 (2.3%)	7 (0.6%)	<0.001
Squamous cell carcinoma	6 (0.1%)	0 (-)	NS
Bowen's disease	13 (0.3%)	0 (-)	0.05
Actinic keratosis	63 (1.5%)	3 (0.2%)	<0.001
Dysplastic naevus	319 (7.7%)	40 (3.3%)	<0.001
Congenital naevus	370 (8.9%)	5 (0.4%)	<0.001
Other cancerous and precancerous lesions	3 (0.1%)	1 (0.1%)	NS

* Including lentigo maligna

NS, not significant.

DISCUSSION

Examination of the entire skin is advocated during the annual skin cancer/melanoma screening programmes supported by the American Academy of Dermatology (AAD).[1,4] The argument is that most malignant melanomas are found on covered skin. During screening clinics in the Netherlands, so far, only lesions specifically presented by the screenees have been evaluated.[6,7] Screening activities in the Netherlands attract large numbers of people. Considering the lack of space and manpower, it is impossible to perform a total skin check routinely on screening participants being concerned about only a single skin mark.

Little is known about the importance and feasibility of complete cutaneous examination during skin cancer screening clinics. Rigel et al conducted a free skin cancer screening particularly to survey this issue.[4] Attendees were asked to fully disrobe, and gown for a complete skin examination. A total skin check was accepted by 1385 of 2239 participants (62%). The yields of the complete and partial examinations were 13 and one malignant melanomas, respectively. It is questionable, however, whether this increase in malignant melanoma diagnoses in the total skin examination group is related to chance detection. The different findings reported by Rigel et al, compared with the findings reported herein, are probably a result of differences in methodology. Rigel et al distinguished between exposed (easy-to-see) and covered (hard-to-see) areas. People who consented to undress completely were categorized as having a total skin exam, as opposed to those having a partial examination of sun-exposed skin only. In our campaign, screenees were asked to show specific lesions that bothered them, irrespective of body area. In addition, they were encouraged to have the rest of their body surface examined. The melanoma patients described by Rigel et al probably opted for examination of covered skin, because they were worried about a skin mark on covered skin.

Lookingbill[8] and Lee et al[9] reported relatively high yields of incidental malignancies found on complete cutaneous examination of dermatology patients. Nearly all tumours were basal cell carcinomas. It is not clear how many of these patients would have shown their hidden tumours anyway as a secondary complaint, irrespective of the opportunity of a total skin check. It has been established that malignant melanomas are regularly shown in passing during office visits for other ailments.[10]

The chance of diagnosing a cutaneous malignant melanoma during additional, total skin examination appears to be extremely low. Only seven cases of low clinical suspicion were recorded, among 1221 persons examined. None of these cases proved to be a malignant melanoma at follow-up. The initial skin check in our campaign

yielded more biopsy-proved malignancies and premalignancies than additional examination of the entire skin. Thirteen malignant melanomas were found, among 4146 screenees. Of these, 12 persons intended to show this specific lesion. Only one malignant melanoma was found in a person who voluntarily opted for total skin examination. In addition, 43 histology-proved basal cell carcinomas, and one case of Bowen's disease, were encountered on initial screening. Of the 1221 persons undergoing additional total skin examination, only three had a biopsy-proved basal cell carcinoma.

In a strict sense, the open access early detection clinics held in Southern Limburg were not screening processes. As public education, self-selection and physician examination may be inextricably intertwined, especially in the case of skin cancer and melanoma,[11] we consider such campaigns as a type of focused and selective screening, focused on the population at the highest risk, and based on self-selection of persons with a high level of awareness and concern. If, however, non-dermatologist physicians are inadequate at identifying pigmented lesions suspicious of being malignant melanomas,[12,13] one may assume that persons at a screening are even worse at this. The AAD experience suggests that people at high risk for skin cancer generally are selecting themselves appropriately to be screened.[14] Non-selective screening of adult women in a high-incidence region (Australia) yielded only one malignant melanoma among 7450 participants.[15] Screening exercises for skin cancer and melanoma produce yields that are considerably higher.[4-6,16,17] It is concluded that focussed and selective screening for skin cancer and malignant melanoma is an easy means of attracting relatively high numbers of positive screenees.

Although the available screening test, the dermatologist's eye, is very accurate in distinguishing malignant from benign pigmented lesions,[12,13,18,19] the small numbers of dermatologists in most Western countries preclude regular, large-scale screening programmes. In order to offer a reliable screening opportunity following a public education campaign, it is imperative to narrow the scope of such screening exercises. Many more screenees can be seen if only index lesions are examined, without routine additional complete skin checks. Adhering to this approach, we have been able to examine 150-200 persons per investigator per day.

Our results indicate that additional total skin examination in people showing specific skin spots during screening for malignant melanoma, is not necessary. A possible exception is the group of attendees exhibiting lesions that are suggestive of malignant melanoma or dysplastic naevi. Disrobing, gowning, and chaperoning, are time consuming. The investment of physician time can be considerable. More screenees

can be seen with limited provider time if only partial skin examinations are performed. This may increase the cost-effectiveness of melanoma screening.

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Chapter 6

VOLUNTEER MELANOMA SCREENINGS: FOLLOW-UP, COMPLIANCE, AND OUTCOME

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Dermatol Surg, in press

SUMMARY

Background: Follow-up information on free melanoma screening clinics is not readily available.

Objective and methods: We studied the follow-up, compliance, and outcome of positive screenees after a screening campaign for melanoma in the Netherlands.

Results: Of the 4146 participants, 486 (11.7%) had a suspicious premalignant or malignant lesion warranting referral to his or her general physician indicating the proposed line of management. Participants with borderline lesions were not referred. Referral of borderline cases should have resulted in a considerable increase of the number of positive screenees (18.1%). All positive screenees but two gave permission for follow-up. Only 18 screenees (3.7%) were lost during follow-up. Moreover, one screenee with a presumed basal cell carcinoma and six screenees suspicious of having a premalignant lesion decided not to seek medical attention despite several reminders. The positive predictive value for melanoma was 17.2%, and for nonmelanoma skin cancers was 42.9%.

Conclusion: A selective referral policy may reduce the generated costs of melanoma screenings substantially. Adequate follow-up of positive screenees is mandatory in order to determine the ultimate yield and usefulness of such campaigns.

Cutaneous melanoma fulfils most basic principles of screening for disease set out by Wilson and Jungner.[1,2] Screening itself gives no health benefit. Diagnostic and treatment services for positive screenees have to be available and positive screenees have to be followed for definitive management. The usefulness and justifiability of screening depends on the extent to which positive screenees can be followed and treated.[3] We studied the referral rate, compliance with referral, the final histopathological diagnosis, and the positive predictive value of a dermatologist's exam in a volunteer screening campaign for melanoma in the Netherlands in 1993.

MATERIALS AND METHODS

In June 1993 a number of voluntary melanoma screenings were conducted in Southern Limburg, the Netherlands.[4] The area has approximately 650,000 inhabitants. All dermatologists in the region participated in this project. The screenees were examined on two consecutive Saturdays at one university hospital and five district hospitals. In the precampaign awareness programme special emphasis was placed only on the risk factors and symptoms of melanoma. Nonmelanoma

one basal cell carcinoma, five dysplastic naevi, and one congenital naevus. These participants decided not to seek medical attention (incomplete follow-up, patient's delay).

Histopathologic examination was achieved in almost all cases with suspected malignancy (162/183; 88.5%). Those with presumed premalignancies were evaluated by histology in 243 of 752 instances (32.3%). Of the 69 persons with presumed melanoma, including lentigo maligna, 64 underwent excisional biopsy. Eleven melanomas were confirmed histologically (positive predictive value, 11/64 = 17.2%). If all suspected cases are included, then the positive predictive value is 15.9% (11/69). Two persons with clinical suspicion of dysplastic naevus proved to have a lentigo maligna and a malignant melanoma in situ, respectively. In summary, there were 13 persons with a pathologically confirmed melanoma (all but one with thickness <1 mm).[4]

Of the 95 persons with suspicious basal cell carcinoma, 81 were biopsied, 36 of which were confirmed by pathologic examination. All six persons with presumptive squamous cell carcinoma were evaluated by biopsy. No squamous cell carcinomas could be proved by histology. Of the 13 persons with presumed Bowen's disease, 11 were subjected to biopsy. None of these was confirmed histologically. Furthermore, eight malignancies were found by histologic assessment, which diagnoses were not considered clinically: seven basal cell carcinomas (clinical diagnoses: squamous cell carcinoma, 1; Bowen's disease, 4; actinic keratosis, 1; and naevocellular naevus, 1) and one Bowen's disease (clinical diagnosis: basal cell carcinoma). The positive predictive value of the dermatologist's visual exam for nonmelanoma skin cancers was 38.6% (39/101) for those referred and 42.9% (39/91) for those biopsied.

Of the 239 persons with dysplastic naevi who received a letter of referral, 200 underwent histologic assessment. In 35 cases dysplastic naevi were confirmed histologically (positive predictive value, 17.5%). Out of the 23 attendees referred because of suspicion of actinic keratoses, 12 were subjected to biopsy and six could be confirmed (positive predictive value, 50.0%).

DISCUSSION

The precise effectiveness, health benefits, and costs of volunteer melanoma screenings are unknown. In this respect, the proportion of those referred among the participants is important. A high referral rate may signify many borderline cases being referred, which increases health care expenditures and decreases the cost-effectiveness of the screening.

Referrals in the present study (11.7%) are in contrast with those in other published studies from the United States[5-8] and Germany[9]. Bolognia et al[5] reported 128 persons out of 251 attendants (50.9%) having a positive screen clinically. In the study of Koh et al[6] 787 out of 2560 screenees (30.7%) had an abnormal exam and were advised to visit their general physician or dermatologist for follow-up. Field et al[7] and Olsen et al[8] described, respectively, 29.8% and 36.2% referrals. Schadendorf et al[9] examined 423 persons during a free skin cancer screening campaign. Out of these, 26.2% were suspicious of having a malignant or premalignant skin lesion warranting referral. Rampen et al[10] reported 10.2% referrals during a number of Dutch screenings carried out in 1990. This percentage corresponds with the referral rate reported in the present study. In both Dutch studies screenees with minimal extent of precursor states or with precursors with low degree of suspicion were not referred in order to avoid unnecessary concern and medical treatment. If all persons with suspicious precancerous lesions had been referred, the proportion of referred screenees in the present study would have been 18.1%.

A more selective referral policy has important implications for the workload of general physicians, dermatologists, surgeons, and pathologists after the screenings. The costs of medical care induced by screening exercises can be reduced considerably in this manner. When lesions with slight suspicion of dysplastic naevus or actinic keratosis are not referred, it is very unlikely that important malignancies will be missed.[11]

The effectiveness of melanoma screening programmes can only be determined when the participants are followed systematically. In the present study follow-up information was obtained from all screenees with suspected malignancy. From those with suspected premalignancy, in all but 18 persons was follow-up information available. Thus, 18 persons (3.7%) were lost to follow-up despite several efforts to contact them by mail or telephone. Moreover, there were seven participants (1.4%) who did not schedule a consultation. Thus, totally 459 of those referred (94.8%) did seek medical care. Our results show the feasibility of adequate follow-up. They compare favourably with the follow-up data reported by Bolognia et al[5] (87.5%) and Rampen et al[10] (90.3%). In the study of Koh et al[6] follow-up information was available in only 63% of all cases; 15% of the referred screenees did not respond and 22% did not schedule a visit with their general practitioner or dermatologist. This discrepancy may partly be due to the differences in the health care system and medical insurance in the Netherlands and the United States. Koh et al speculate that 'persons who failed to comply either had no regular health care provider or dermatologist or did not know how to obtain proper treatment'.[6] Bolognia et al[5] describe in their paper various reasons given for not seeking recommended care:

concern about a benign lesion but not the suspect lesion, only wanting reassurance that they did not have melanoma, and lack of insurance. Recently, Koh et al[12] presented follow-up particulars of the American Academy of Dermatology-sponsored skin cancer screenings. Only information about screenees suspicious of having melanoma was given. Out of 4458 positive screenees, 174 (3.9%) persons could not be traced for follow-up and 903 (20.2%) screenees did not visit their physician for further advice. The authors suggest that more adequate follow-up can be achieved by using a centralized follow-up system. In the Netherlands we also have the experience that follow-up results are more complete when they are collected centrally.

In most published studies, the yield of skin cancer and melanoma screening has been reported in terms of presumptive clinical diagnoses. Few studies have included details of pathologically confirmed malignancies.[5,6,10,13] In the present study, especially those attendants with presumed malignancies were evaluated by histology (162/183; 88.5%). Those with presumed precursors were evaluated by histology in only 243 of 752 instances (32.3%). The scope of any screening exercise ends with histopathological assessment of subjects positive on screening, followed by appropriate treatment. Skin biopsies are important outcome measures of total yield, positive predictive value, and cost-benefit ratio of the screening. Final assessment and treatment in a structured manner are crucial ingredients of skin cancer and melanoma screening campaigns.

The value of volunteer screening for skin cancer largely depends on the numbers of melanomas detected. Rigel et al[13] found 14 suspicious malignant melanomas among 2239 screenees (0.6%). All these lesions were histopathologically confirmed. Interestingly, there appeared to be no false-positive screenees. Koh et al discovered 9 malignant melanomas among 2560 screenees (0.4%). Bolognia et al failed to detect any melanomas among 251 screenees[5], and Rampen et al[10] found six histology-proven melanomas, including one lentigo maligna, among 2564 screenees (0.2%). In the present study 13 melanomas were histologically confirmed among 4146 participants (0.3%).

In the present study only 11 melanomas out of 64 biopsied suspicious lesions could be histologically confirmed. This is due to the fact that many lesions with low suspicion were included in the presumptive diagnosis group. Therefore, the positive predictive value for melanoma is low (17.2%). When only the first diagnosis is considered the positive predictive value for malignant melanoma (including lentigo maligna) increases to 34.4% (11/32). Koh et al[12] found 364 confirmed melanomas out of 3237 lesions biopsied (11.2%). Clinical diagnoses included melanoma and

"rule out melanoma". When only melanomas were considered the predictive value increased to 17.0%.

Squamous cell carcinoma seems to be difficult to diagnose clinically. None of the presumed cases of squamous cell carcinoma and Bowen's disease in our series were histologically confirmed. The final diagnoses of the suspected squamous cell carcinomas were: one basal cell carcinoma, two actinic keratoses, one seborrhoeic keratosis, one keratoacanthoma, and one pseudoepithiomatous hyperplasia. On the other hand, basal cell carcinoma has distinct clinical characteristics, which results in a relatively high positive predictive value (in this study 44.4%).

It should be realized that different definitions have been used for calculating the positive predictive value. Koh et al[6] give two different positive predictive values: one low value for true positives/total screened and a higher value for true positives/total followed. The positive predictive value reported by Bolognia et al[5] was based on histologic confirmation of lesions that were biopsied. Rampen et al[10] reported two values for all suspected skin cancers: one low value for those histologically confirmed out of those referred and one higher value for those histologically confirmed out of those followed ('including and excluding defaulters').

Elwood[14] emphasizes that nonmelanoma skin cancers require only simple treatment and have excellent prognosis. Thus, the argument for skin cancer/melanoma screening needs to be made primarily for melanoma. If the whole programme is justified only as melanoma screening exercise, the predictive value is calculated as melanomas confirmed/total screenees followed. In that case, the positive predictive value in our series is only 2.8% (13/459).

Differentiating early melanomas from dysplastic naevi can be very difficult. This has been shown in two of our screenees: one suspicious dysplastic naevus proved to be a lentigo maligna and another one proved to be an in situ melanoma. This illustrates one of the potential hazards of screening in general and melanoma screening in particular: false-negative screens may delay future consultation because of a false feeling of safety. Screenees must be made aware of the fact that a negative screen does not guarantee that the person will not develop melanoma in the (near) future.

More appropriate selection of referrals for further management theoretically decreases work load and costs of medical care induced by screenings. In this way the number of false-positive results can be minimized and unnecessary biopsy and surgery can be avoided. This can partly be achieved by excluding from referral those with questionable disease or minor precursor states. Selective referral can also be achieved by adding of a second discriminatory test to the primary screening test.[3] The

screening test used so far in skin cancer and melanoma screenings is the trained eye of the dermatologist. The use of the dermatoscope can be advocated as an additional measure for screening pigmented skin lesions.[15,16] Thus, the number of participants who are referred for skin lesions of questionable importance could possibly be diminished. However, several questions about the proper value of the dermatoscope in general have to be solved before this technique can be recommended in screening settings.

Further refining of referral procedures might increase cost-effectiveness of volunteer melanoma screenings. Almost complete follow-up is feasible with the use of a centralized follow-up system. The work load of follow-up is time consuming. Yet, follow-up is an inherent part of the screening procedure. A more uniform approach to evaluate screenings is also necessary to compare results in different studies. Although, it has to be taken into account that the outcome of volunteer screenings is also dependent on the specific circumstances such as the health care system of the country where the screenings are held.

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Chapter 7

SCREENING FOR MELANOMA: WATCH THE EARLY BIRD!

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SUMMARY

It may be questioned whether people attending skin cancer and melanoma screening clinics are sufficiently aware of their own risk profile. In June 1993, 4146 people were examined in Southern Limburg, the Netherlands, during a voluntary melanoma screening project. Positive screenees, i.e. those with presumed malignancies or with distinct precursor lesions, attended early during the day rather than late. This indicates that people with cancerous or precancerous skin lesions are, on the whole, sufficiently concerned as to take maximum advantage of the screening opportunity. Our findings also imply that abundant provider time and staffing are necessary during the early hours of such screenings.

Screening for melanoma and other skin cancers is recommended and practised in many countries. Screening is especially worthwhile for high risk groups. So far, skin cancer and melanoma screening programmes have been based on public education campaigns followed by free consultation. It may be questioned whether the general public is sufficiently capable of purposeful self-assessment.[1-4] Despite adequate precampaign educational messages, screening programmes produce large numbers of negative screenees. There is a risk of overtreatment, anxiety, and increased health system costs. Therefore, we need data to demonstrate that persons who voluntarily attend melanoma/skin cancer screenings are, on the whole, at risk for the disease. In 1993 we conducted a number of free melanoma screening clinics in Southern Limburg, the Netherlands. The main aims of the project were to investigate: (1) the value of screening for melanoma only, instead of screening for skin cancer in general; and (2) the extra yield of total skin examination additional to examination of specific lesions the attendees are worried about. More or less fortuitously, we noticed that people with cancerous or precancerous lesions attended relatively early in the morning, and that the rate of trivial lesions increased during the day. The workload was highest during the morning sessions and decreased in the afternoon. These observations may indicate that participants who appraise their lesions with accuracy, are maximally motivated to attend the screenings. In addition, our findings may have practical implications regarding staffing of the screening exercises. The present study was initiated to address these points.

MATERIALS AND METHODS

In June 1993 ten, free melanoma screening clinics were held in Southern Limburg, the Netherlands. The screenings took place over two consecutive Saturdays. All

dermatologists in the region participated in this project. The area has a population of approximately 650,000.

At each clinic, attendants were divided into three equal groups, the early and late-comers at both ends, and an intermediate group. Because of the retrospective nature of the study we were unable to ascertain the precise time of first and last attendances in each group.

All clinically suspicious malignancies were recorded. Diagnoses included were: melanoma, lentigo maligna, basal and squamous cell carcinoma, and Bowen's disease. All patients with presumptive malignant lesions received a referral letter. Precursor states were divided into two groups: those with borderline lesions and those with more obvious disease. The attendants in the first group were advised to see a doctor in due course on their own initiative. The persons in the latter category were given a letter of referral for their general physician to secure proper treatment at their earliest convenience. Diagnoses included were actinic keratosis, dysplastic and congenital naevus, and sebaceous naevus. Persons with clinically suspicious skin cancer and those with clear evidence of a precursor state warranting referral, comprised the positive screenee group. Negative screenees were those with borderline precursor lesions and those with benign skin marks.

After 4 months and again after 10 months the screen-positive participants were followed. To this end the positive screenees were contacted by letter or telephone, dermatologists were asked for treatment and pathology particulars, and the Dutch national pathology data bank (PALGA) was scrutinized for cancerous and precancerous diagnoses among the positive screenees. Completeness of follow-up of positive screenees was 95%.

Statistical significance of differences between the groups was assessed using the non-parametric test of Kruskal-Wallis. When appropriate, statistical significance of trends was tested by using logistic regression.

RESULTS

There were 4146 attendants with evaluable records. Of these, 1381 were categorized as early-comers, 1380 were in the intermediate group, and 1385 were late-comers. Relatively more positive screenees came early, whereas innocuous lesions were more often seen late. In Table 1 the screenees are grouped by clinical diagnosis and according to time of presentation. More presumptive cancerous and distinct precursor lesions were seen early during the screenings ($p=0.03$). This trend was observed during both screening days and was very consistent at almost all screening locations. The

total number of referrals (positive screenees, i.e. presumptive malignant lesions and distinct precursor lesions combined) decreased from 190 in the early group to 139 in the intermediate group, and to 117 in the late group ($p<0.001$).
Table 1 also presents the follow-up data of positive screenees. Histologically confirmed melanomas and nonmelanoma skin cancers are shown separately. More melanomas and nonmelanoma skin cancers were found among the early-comers as compared with the later groups ($p=0.006$). Numbers include melanoma in situ and carcinoma in situ. As for melanoma only, the trend of decreasing incident cases during the day did not reach statistical significance ($p=0.10$). Small numbers, however, preclude meaningful statistical analysis. All but one melanomas were of favourable microstage (Breslow thickness <1 mm).

Table 1. Particulars of screenees according to time of attendance

Time of attendance	Early n=1381	Intermediate n=1380	Late n=1385	Significance (p)
Clinical diagnosis				
Malignant lesion	68 (4.9%)	61 (4.4%)	42 (3.0%)	
Precursor lesion, distinct	122 (8.8%)	78 (5.7%)	75 (5.4%)	
Precursor lesion, borderline	106 (7.7%)	138 (10.0%)	34 (9.7%)	
Benign lesion	1085 (78.6%)	1103 (79.9%)	1134 (81.9%)	0.03*
Histologic diagnosis				
Melanoma	7 (0.5%)	4 (0.3%)	2 (0.1%)	0.10**
Nonmelanoma skin cancer	20 (1.4%)	14 (1.0%)	8 (0.6%)	0.03**
Total	27 (2.0%)	18 (1.3%)	10 (0.7%)	0.006**
Fear of skin cancer	408 (29.5%)	354 (25.7%)	349 (25.2%)	0.01**

* Kruskal-Wallis test
** Logistic regression.

Fear of having skin cancer was an important reason to attend the screens in 1111 persons (26.8%). Early-comers admitted fear of skin cancer more often than screenees in the intermediate and late groups (Table 1; p=0.01).

DISCUSSION

Screening on the basis of self-selection appears to be a suitable method for the early detection of melanoma and nonmelanoma skin cancer. How accurate self-screening is, depends largely on the appropriateness of precampaign public educational programmes. Promotional strategies should attract the proper target population.

There is some doubt about the ability of the general public to appraise skin lesions as risky.[1,2,4] This is not surprising since reliable interpretation of warning signs of melanoma may be extremely difficult for even non-dermatologist physicians,[5-7] and even for dermatologists.[8,9] Girasek noticed that attendees of skin cancer screening clinics were unable to attribute their high risk status to their symptoms.[1] She also found that positive screenees were no more likely than negative screenees to seek medical attention of their own volition, had a screening opportunity not been offered. Likewise, Weinstock emphasized that the screenee's perception that a melanoma warning sign or risk factor is present, may be inaccurate.[2] On the other hand, there are literature data suggesting that high risk persons are, in general, sufficiently aware of their own risk profile.[3,8]

Rather by chance we noticed that during a screening project in 1993 relatively more malignancies were diagnosed during the early hours of the screenings. The workload was highest during the morning sessions. These observations prompted us to conduct the present investigation. Our findings indicate that positive screenees are, on the whole, more seriously worried about their skin lesions than screen-negative persons. They apparently visit the screening location as soon as it suits them in order to take maximal advantage of the screening. Another interpretation might be that those individuals who get up early are at higher risk of developing skin cancer. This possibility seems most unlikely.

We also noticed that screening concentrating on melanoma, instead of skin cancer in general, increases the numbers of lesions suggestive of melanoma and dysplastic naevi.[10] This implies that people attending in response to multimedia publicity efforts seem to be at appropriately high risk.

One may argue that at the beginning of the screening exercise dermatologists display greater alertness or have a lower referral threshold, which causes a higher referral rate. If that was the case then the number of false-positive screenees would be highest

among the early-comers and the number of true-positive screenees (proved by histology) would be more or less equal in the three groups according to time of attendance. In fact, the rate of true positives decreased steadily during the day. Moreover, fear of cancer was more often recorded by the early-comers than by the late-comers. In previous skin cancer screening campaigns in the Netherlands we encountered very low false-negative results (three out of 1551 persons followed).[11] These findings indicate that the trends reported herein are screenee-dependent and not screener-dependent.

We noticed that during the morning sessions more persons per hour were attending than in the afternoon. Added to this, the rate of positive screenees was highest in the early hours. Screen-positive persons need more thorough examination, they have to be advised and reassured, referral notes have to be written, et cetera. This has definite practical implications. One of the most fundamental prerequisites of skin cancer and melanoma screening campaigns is the optimal organization of the screens.[12,13] High attendance rates and increased positive findings during the first hours of the screening necessitates abundant provider time, extra auxiliary personnel, and ample examination rooms.

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Chapter 8

GENERAL DISCUSSION AND CONCLUSIONS

Cutaneous melanoma causes a considerable morbidity and mortality worldwide. The peak occurrence of superficial spreading melanoma and nodular melanoma lies between 40 and 50 years of age. Consequently, it mainly affects younger people. Many decades the early signs and symptoms of cutaneous melanoma are well documented. Theoretically, every melanoma can be detected in an early stage while it is thin and curable. It has been shown that surveillance of groups of people at high risk of melanoma results in detection of melanoma at an earlier stage than otherwise would occur. Public education programmes targetting on those at highest risk (skin phenotype, family or personal history of melanoma, multiple and/or dysplastic naevi) may have the same effect. Melanoma screening as a measure of secondary prevention can be organized at low costs. The screening tool, the trained eye of the dermatologist is an inexpensive, safe, reliable and generally accepted means of early detection. The melanoma screenings in Southern Limburg were visited by many self-selected participants. Dermatologists did the skin checks and determined which screenees should be referred for further advice. This is necessary to avoid too much strain on the services of general physicians. The screenings could be organized easily in the existing Dutch health care system. Future campaigns can be refined and improved further.

What does volunteer screening mean? The present study is based on the results of a public education campaign focusing on melanoma, followed by open access clinics or 'skin check' sessions in June 1993. In the literature public education campaigns combined with such open access clinics have been described as 'screenings', 'screening clinics', 'volunteer screenings', 'targeted screenings', and 'free screenings'. Actually, the use of these terms is not correct because in a strict sense these open access clinics are not genuine screening interventions.[2] Participants are not selected from population listings as is the case in mammary or cervical cancer screenings. Participants of open access clinics are self-selected. They attend the clinics because of their skin phenotype or risk factors (screening) or because of suspicious skin spots (case finding). Thus, the use of the term 'screening' is rather misleading. We consider these campaigns as a type of volunteer targeted and selective screening, focused on the population at the highest risk and based on self-selection. The target group is recruited by selective announcements during the publicity campaign.

What is the most ideal period? Early summertime is the most ideal period to organize such campaigns. In this period people wear lighter clothing and are probably more

aware of any skin problems.[3] Furthermore, during the summer period dermatologists, who form the most reliable screening test (visual examination of the skin), are generally less busy.

Who should perform the screenings? Only dermatologists or senior residents in dermatology performed the examinations during the Southern Limburg campaign. Several studies show that dermatologists are best trained in recognizing (early) melanomas and differentiating melanomas from other pigmented skin lesions. Missing a melanoma has important implications. Ideally, false-negative findings should be reduced to virtually zero, which cannot be guaranteed by non-dermatologists. Overdiagnosing suspected skin lesions, (false-positive screens), on the other hand, leads to undue concern and overtreatment and induces substantial costs.

At what location should be screened? Most screenings so far in the Netherlands have been carried out in outpatient dermatology departments of university or district hospitals. Although we feel that these locations have distinct advantages, some authors believe that free skin cancer detection clinics should be carried out in public buildings like libraries or schools, or at health fairs.[4] Screening clinics should never be undertaken for the benefit of any specific physician or hospital. Therefore these authors believe that such clinics should not be carried out in private offices or hospitals. On the other hand, hospitals are familiar to the general public, there is abundant space to park and they can be reached by public transport rather easily. Outpatient dermatology departments have waiting-room facilities and sufficient examination rooms. Most importantly, outpatient dermatology departments are well equipped and adequately lighted for skin examination purposes.
Beach locations are less suitable. Although beaches seem very appropriate for primary prevention interventions, we feel that such locations have clear disadvantages with regard to early detection exercises. When screening at the beach is considered, special facilities have to be provided, which induces extra costs. Furthermore, screening at the beach never has a local or even regional character which might interfere with adequate follow-up and evaluation of positive screenees.

What is the role of the general practitioner? In our project, the general practitioners were notified about the campaign by personal mailings. Furthermore, a special informative meeting had been organized. Only 20 out of 350 general practitioners in the Southern Limburg area attended this meeting. In the programme emphasis was placed on pigmented skin lesions, especially (early) melanoma and its precursor

lesions. Attention was also paid to populations at risk to develop melanoma. Such a meeting focusing on secondary prevention serves important educational goals. General practitioners do not see many melanomas. Theoretically, educational messages may improve their skills. However, a British study showed that education of general practitioners did not influence the early detection of melanomas; only after education of the general public on the early signs and symptoms of melanoma more and thinner melanomas were detected.[5,6] Nevertheless, general practitioners see many pigmented skin lesions in their daily practice. They can give information about early signs and symptoms and risk factors of melanoma. Conceivably, the information given can be optimalized by illustrated leaflets and brochures.

Which publicity channels are most relevant? The aim of the present publicity campaign and the open access clinics was announced through pamphlets and through articles in the regional newspapers and periodicals. The voluntary screenings were held in a more or less secluded area of the netherlands: Southern Limburg. General practitioners and pharmacists were asked to expose pamphlets in their waiting rooms. The pamphlets were also exposed in public libraries and hospitals. In the future other locations should be considered like banks, sport facilities, schools, post offices, and railway and bus stations. In the Southern Limburg study only the regional newspapers and neighbourhood periodicals were approached for the precampaign announcements and proved to be most important. It can be expected that, in the context of a national screening intervention, the precampaign awareness programme will have more impact when also the national newspapers and the national radio and television stations are used.

Which target groups should be focused upon? The message should be a positive one. When melanoma is found and treated early, total cure can be obtained. An aggressive approach will induce unnecessary concern. In the publicity campaigns one of the unique properties of melanoma must be emphasized: It is an easily visible tumour. Many melanoma patients are aware of the existence of specific skin spots. Special vigour should be given to the early changes and symptoms of melanoma. Delay is usually not caused by fear or ignorance but more by lack of knowledge.[5,7] Several studies show that late symptoms such as pain and bleeding are more concerning than early warning signs such as changes in colour and size.[8-10] Interestingly, in the formal leaflets of the Dutch Cancer Foundation ("Acht goede redenen om naar de dokter te gaan", 1994) pain and bleeding of pigmented skin lesions are listed first. Temoshok showed that persons with little or no knowledge

about melanomas tended to develop thicker lesions.[11] Also people with tumours on difficult to see areas often present later. Self-examination of the skin has great significance.[12] So far during the campaigns in the Netherlands these items have not been especially focused upon. They may be of particular importance when developing new programmes.

Various groups in the general population are at more than average risk to develop melanoma because of their skin phenotype (blond hairs, blue eyes, freckling, burning tendency), because of more than average mole counts, or because of a personal or family history of melanoma. Theoretically, there are other groups at special risk because of their known 'less awareness' of melanoma (e.g. men, elderly persons, and single persons).[13] Also in the present study less men attended the screenings and they were prompted more often by relatives or friends to attend.[14] Further studies are necessary to demonstrate whether it is worthwhile to focus education campaigns especially on these risk categories.

Is screening for nonmelanoma skin cancer worthwhile? The major objective of (volunteer) screening is reducing mortality and morbidity by finding disease and starting effective treatment at an earlier stage. Although nonmelanoma skin cancer is an important health problem, the benefit of screening is very doubtful. Nonmelanoma skin cancer has a low mortality rate. The problems which may result from these skin tumours are totally different from those of melanomas and need their own approach. We feel that the nonmelanoma skin cancers should not be a subject for screening. In the present study it was shown that relatively more melanomas and atypical naevi could be detected against less nonmelanoma skin cancers and benign skin lesions after a precampaign awareness programme focusing on melanoma only.[15]

What is the role of ultraviolet (UV) light? Since the precise cause of melanoma is not known, it is not easy to develop primary prevention programmes on melanoma. Avoidance of and protection against UV radiation is an important measure to curtail the development of nonmelanoma skin cancer. In several public education campaigns also emphasis is placed on the role of sun protection to prevent melanoma. Yet, there are many unsolved issues in the possible role of UV in the aetiology of melanoma. There are potential dangers when the possible causal role of UV in the development of melanoma is emphasized too much. Especially those people who avoid sun exposure or those who discover lesions on sun protected areas are at risk of delayed diagnosis.[16,17]

What about total skin examination? In the present study the general public was offered a free skin check by a dermatologist. The clinics were organized in such a way that a maximum of attendees could be examined with a minimum of provider time (estimated 150-200 persons per dermatologist per day).[18] Only specific skin lesions the attendees were worried about were examined. In 1385 attendees an additional total skin check was offered. This proved to have only a minimal yield. No melanomas were detected at additional total skin examination.[19] It can be expected that future campaigns can be more efficient when complete skin exams are performed selectively.

Are there other practical considerations? Many positive attendees visited the open access clinics early during the day.[20] They seemed to be able to select themselves appropriately and were maximally motivated to attend the screenings. Abundant staff should be available during the morning hours to limit waiting time. Watch the early bird!

Which screens should be regarded as positive? During the open access clinics no diagnostic or therapeutic procedures were performed. When subsequent examination or treatment was necessary the attendees received a letter of referral to their general practitioner with the proposed line of management. Thus, only approximately 10% of all screenees used the regular health care facilities. The referrals were selected carefully and unnecessary referral or treatment of those with minimal extent of disease (borderline cases) was avoided. An unmanageable strain on the general practitioners' services is unlikely.[21] The same applies to the pathologists' workload generated by melanoma screening campaigns.[22] In the United Kingdom in 1986 several publicity campaigns for melanoma without screening clinics were organized. Because of the strain put on the health services it was decided that these campaigns should not be continued.[24]

Should screening be organized periodically? Ideally: yes. Screening should be a continuing process and not a single occasion activity.[23] There is no useful information on the optimal frequency of melanoma screenings (once every 2 years?). A potential danger of periodic screening is delay of people who possibly postpone their appointment knowing a free screening is coming.

Is follow-up necessary? In the Southern Limburg project we adhered to a strict follow-up protocol. When the screen-positive participant had given permission, follow-up

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was accomplished. Follow-up particulars about the recommended visit to the general practitioner and, when appropriate, the outcome of histological examination were collected. This follow-up has been performed by the author by visiting the regional dermatologists and by phone calls and mailings. Only 18 referred screenees (3.7%) were lost during follow-up.[25] Overall, compliance with referral was adequate. Although this elaborate type of follow-up has been proved to be extremely efficient, it is most time consuming. In future screenings, this part of the screening intervention has to be developed further. Dermatologists who examine or treat positive attendees should also contribute to the compilation of follow-up data. Only with adequate follow-up of positive screenees the ultimate yield and usefulness of such campaigns can be determined. Follow-up must be considered as an inherent part of screening.

What are the ethical and legal aspects of screening? Combined public education campaigns and screening sessions have potential hazards. Not all participants will benefit from the screening. First, there is the problem of the false-positive screens. These attendants undergo unnecessary diagnostic and treatment procedures. On the other hand, there may be false-negative participants who are given a false feeling of safety. In this respect it is encouraging that no melanomas were missed during a previous campaign.[26] Furthermore, participants have to be made aware of the fact that a negative skin check is no guarantee that skin cancer will not develop in the future. These possible complications, risks, and limitations have to be explained to the attendants of skin check clinics.

How much will volunteer melanoma screening cost? The present study was supported in part by a grant from the Comprehensive Cancer Centres IKO (Nijmegen) and IKL (Maastricht). Our programme has been inexpensive because volunteer dermatologists, residents, and health care professionals participated in the project. There are many hidden costs: the organization of the screenings, the guidance of screeners and auxiliary personnel, the follow-up of positive screenees, the costs of hospital facilities and services, and the induced expenses for positive screenees. Further evaluation of public education programmes with selected referral is necessary to determine cost-effectiveness. Costs must be weighed against benefits. Theoretically, the benefits are decreased mortality and morbidity, savings in the use of health care resources, improvement of quality of life, and increase of economic productivity. The main question remains: Who should pay for this? The consumers, the health insurance companies, the government?

How can we educate the general public about early signs and symptoms of cutaneous

melanoma, at minimal costs and a maximal yield in terms of thin melanomas? Public education programmes on melanoma without subsequent skin check sessions seem to have important effects on the number of self-referrals to general physicians and dermatologists. This may induce extra costs and unnecessary treatment and concern. Theoretically, the Southern Limburg study provides a new approach in which an education campaign is complemented by a free volunteer screening of those at highest risk by dermatologists at minimal costs. As a result of this selection of referrals much unnecessary treatment can be avoided.

Conclusions: Studies according to the American Academy of Dermatology model carried out so far in the Netherlands show that they are feasible and seem to fulfil a need. Screening should concentrate on melanoma only. The rationale of screening for nonmelanoma skin cancer is debatable. Total skin exams, additional to the assessment of specific index lesions people present with, are time consuming and not yielding.
The organization of volunteer screening interventions on melanoma encompasses adequate follow-up and treatment of positive screenees. Evaluation in terms of treatment outcome is essential. Screenings are carried out within existing health care facilities. In the Netherlands there are regional Comprehensive Cancer Centres, and there is a national registry for pathology reports (PALGA) which makes it possible to organize and implement new programmes. It is relatively easy and very attractive to develop these secondary prevention programmes further. Future studies should be set up in cooperation with dermatologists, epidemiologists, health education specialists, general physicians, pathologists, and the Comprehensive Cancer Centres. Health economists, the Dutch Cancer Foundation, and governmental bodies should also be involved in future programmes.
A word of caution on provider time is necessary. It is our experience that regional screening exercises can be appropriately staffed by dermatologists if two days (consecutive Saturdays) are scheduled. Large scale, national screenings with an appeal to the national publicity channels may result in a much larger attendance than in the previous campaigns and provider time may turn out to be insufficient.
Up to now self-selected melanoma screenings in the Netherlands have been pilot studies. Only after more insight has been achieved into the cost-effectiveness of volunteer melanoma screenings, such prevention interventions can be introduced on a larger (national) scale and/or on a regular basis (once every 2 years?). In any case, close cooperation between national governmental departments and anti-cancer councils on the one hand, and practising dermatologists on the other hand is regarded as a sine qua non.

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APPENDIX

ORGANIZATION OF A VOLUNTARY MELANOMA SCREENING CAMPAIGN

The present study describes voluntary melanoma screenings in a more or less secluded area of the Netherlands, Southern Limburg. The screenings were carried out under de auspices of the Dutch Society of Dermatology and Venereology and the Comprehensive Cancer Centres IKO (Nijmegen) and IKL (Maastricht). All activities were initiated and coordinated by a relatively small group of highly motivated people. When national programmes are planned, national cancer societies and governmental departments might be important sources of cooperation and publicity.

Any secondary prevention intervention on melanoma must be based on self-examination and self-referral of persons at risk. Approaches to public education and consecutive screening may vary considerably according to the health care system in the relevant country: family physician-based versus specialist-based.

Family-doctors may act as initial screeners in countries with a specialist-referral service rather than a specialist-based service, such as Britain. In countries with major specialist health care facilities, such as the United States, voluntary melanoma clinics may offer open access to dermatologists.
Theoretically, the general practitioner network may filter much of the workload which is generated by the screening. On the other hand, clinical diagnosis is less accurate and the rate of false-positive and false-negative screens will increase.

The following schedule of a public education campaign and screening exercise is largely based on the establishment of open access screening facilities run by dermatologists.

TIME TABLE

12-15 mo • Decide on how and when to launch the campaign:
- regional? national?
- one month? one week? one or two weekends?
- spring or early summer is probably the best period of the year.

10-12 mo
- Inform local dermatologists and/or the national dermatology society of the plans.
- Approach regional and/or national cancer societies or other cancer organizations for their help.
- Approach health care ministry or other governmental bodies and invite their assistance.
- Appoint a campaign manager.
- Start fund raising and co-sponsoring.

6-10 mo
- Fix campaign date(s):
  - be sure that dates do not clash with national holidays.
- Prepare dermatologists' conference and encourage appropriate participation.
- Formulate issues for research.

4-6 mo
- Prepare leaflets and posters.
- Compile lists of participating dermatologists/centres, community organizations that might assist, and newspapers and broadcast media.
- Supply local dermatologists with an overview of all the planning activities, including a complete time table:
  - secure tight organization,
  - focus attention on melanoma and dysplastic naevi,
  - total body examination or not?
  - guidelines for referral,
  - emphasize adequate follow-up,
  - encourage research activities.

2-4 mo
- Prepare screening forms, questionnaires, and referral letters.
- Organize instructive meeting for dermatologists.

Local activities:
- Prepare general physicians' conference and encourage appropriate participation.
- Appoint programme director for each screening location.
- Establish contact with the hospital service, or other representatives to plan screening site, auxiliary personnel, and routing.
- Recruit volunteers.

1-2 mo
- Secure final arrangements regarding preparation of leaflets, hand-out materials, posters, and screening forms.

Local activities:
- Prepare any press releases.

2-4 wk
- Send posters to screening clinics to be distributed in the respective areas.
- Coordinate publicity efforts.

Local activities:
- Secure abundant facilities:
  - examination rooms,
  - auxiliary personnel,
  - traffic flow and sign-posting.
- Send free posters to general physicians, pharmacies, community organizations, and public places.
- Organize information meeting for general physicians:
  - lecture format on signs and symptoms of melanoma and precursor lesions,
  - instruction and discussion format on prerequisites, goals, and organization of the screens.

1-2 wk
- Confirm all arrangements with screening sites.
- Send support and hand-out materials to screening sites.
- Conduct interviews in regional and/or national newspapers, and on regional and/or national radio and television.

Local activities:
- Organize instruction meeting for auxiliary personnel.
- Confirm all local arrangements.
- Secure that all information materials and screening forms have arrived.
- Arrange local interviews and other press releases.
- If only local/regional screenings are planned:
  - inform dermatologists from adjacent areas about the programme.

DATE(S) OF SCREENING

1-2 wk after

- Confirm that screening forms and questionnaires from all clinics have returned.
- Send thank-you notes to participants.
- Contact all participating dermatologists to stimulate follow-up activities.

Local activities:

- Send thank-you notes to all volunteers and other participants.
- Assess results of the screening itself:
  - numbers of attendants,
  - numbers of positive screens (melanoma, nonmelanoma skin cancers, precursor lesions),
  - any problems encountered.
- Prepare press announces on preliminary results.
- Be sure that all forms are send to the campaign manager or central organization.
- Start follow-up of positive screenees with presumed melanoma or other important/metastasizing tumours.

2wk-2mo after

- Evaluate results of the screening.

Local activities:

- Complete follow-up of positive screenees and send follow-up data to campaign manager/central organization.

> 2 mo after

- Collect follow-up data.
- Assess final results, including follow-up.
- Contact media for press releases on final results.
- Report on final results and recommendations, and, if applicable, on research findings.

Local activities:

- Further follow-up: optional.

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SUMMARY

In this thesis the results are described of a volunteer melanoma screening campaign in Southern Limburg, the Netherlands, in June 1993.

Chapter 1. The introduction deals with some general aspects on cutaneous melanoma. Successively, the epidemiology, classification, clinical signs and symptoms, differential diagnosis, staging and prognostic factors, treatment, follow-up, and precursor lesions of melanoma have been briefly reviewed. Cutaneous melanoma is an easily visible tumour that can be recognized and treated early, in a stage with excellent prognosis.

Chapter 2. The fundamentals, methods, advantages, and limits of secondary prevention programmes for skin cancer in general and melanoma in particular are discussed. Public education campaigns followed by free screening sessions for those at highest risk, offer particular challenges with regard to skin cancer and, especially, melanoma.

Chapter 3. The characteristics and motives of attendees of volunteer melanoma screenings are analyzed in this chapter. Females predominate over males, especially in the 20-49 age group. Most participants intended to show only one or a few specific lesion(s). The newspapers represented the most important publicity channel to participate. Important reasons to visit the clinics were: getting more information on skin cancer, and fear of having skin cancer. Future screening interventions should predominantly target the male population.

Chapter 4. The outcome of the volunteer skin cancer/melanoma screenings in 1990 are compared with the results of the focused melanoma screenings in 1993 in Southern Limburg. The latter campaign yielded a more selective attendance in terms of more suspicious melanomas and dysplastic naevi, and less nonmelanoma skin cancers, actinic keratoses, and benign skin lesions.

Chapter 5. Additional total skin examination during screening for melanoma does not increase the detection rate. Among 1221 persons having complete skin exams

additional to examination of intentionally shown skin lesions, no melanomas were encountered. Only 3 basal cell carcinomas were detected. It is concluded that total skin examination during melanoma screening is not worthwhile.

Chapter 6. The feasibility of adequate follow-up, and the outcome of positive screenees after the volunteer melanoma screenings are described. In this study, compliance with follow-up was appropriate. Refining the referral and follow-up procedures seems to be necessary.

Chapter 7. During the melanoma screenings it was noticed rather by chance that relatively more malignancies were diagnosed during the early hours of the screenings. Analysing the histological data the clinical results could be confirmed. This suggests that persons with skin cancer or melanoma are, on the whole, sufficiently concerned as to take maximum advantage of the screening opportunity. Our findings have also practical implications with regard to staffing of the screenings.

Chapter 8. In this summarizing chapter several unique properties of the volunteer melanoma screening concept in the Netherlands are discussed. One striking point is the fact that the campaign has been organized within the existing facilities of the Dutch health care system. It is tempting to speculate about future extensions of this concept. Before any decisions as to large-scale, national campaigns can be made, one must be fully familiar with the principles and practice of these volunteer melanoma screenings. Screening for melanoma has to be evaluated on its own merits. Additional multidisciplinary studies may finally determine whether the present concept is cost-effective and a reliable and justifiable approach to control cutaneous melanoma.

SAMENVATTING

Hoofdstuk 1. Het melanoom van de huid is een vorm van huidkanker. Het wordt ook wel kwaadaardige moedervlek genoemd. Hoewel het basaalcel- en plaveiselcelcarcinoom van de huid veel vaker voorkomen, is de mortaliteit van het melanoom het hoogst van alle huidmaligniteiten. In Nederland overlijden er bijna 400 mensen per jaar aan de gevolgen van deze vorm van huidkanker. Dit heeft onder andere te maken met het feit dat het melanoom reeds in een vroege fase kan metastaseren. Ondanks enkele decennia van intensief onderzoek, zijn er (nog) geen succesvolle behandelingen ontwikkeld voor het hematogeen gemetastaseerde melanoom. Vooralsnog zijn op dit moment alleen vroege ontdekking en chirurgische behandeling van de primaire tumor de belangrijkste wapens.
Het melanoom van de huid heeft de unieke eigenschap dat het een maligniteit is die aan de 'buitenkant' zit en voor iedereen zichtbaar is. Reeds jaren zijn de vroege kenmerken van een (zich ontwikkelend) melanoom bekend en kunnen worden samengevat in de ABCD-regel (Asymmetry, Border, Colour, Diameter): asymmetrie van de afwijking, onregelmatige randen, wisselende kleurschakeringen: bruin, blauwzwart, roze-rood, wit, en diameter >6 mm. Theoretisch zou het mogelijk moeten zijn dat een melanoom door zowel medici als niet-medici in een vroege fase wordt opgemerkt en herkend. In deze fase is behandeling eenvoudig (poliklinische ingreep onder plaatselijke verdoving) en de kans op genezing heel groot.
In dit inleidende hoofdstuk worden enkele algemene aspecten van het melanoom beschreven, waaronder de epidemiologie, classificatie, klinische kenmerken, differentiële diagnose, prognostische factoren, behandeling en follow-up. Verder wordt aandacht besteed aan de belangrijkste precursors van het melanoom: de congenitale naevus en de dysplastische naevus.

Hoofdstuk 2. In de loop van de jaren zijn er wereldwijd verschillende strategieën ontwikkeld om melanomen in een vroegere fase te ontdekken. Deze zogenaamde secundaire preventie-programma's bestaan uit publieksvoorlichting alléén (Engeland) of uit publiekscampagnes en open dagen met onderzoek en advies door een dermatoloog (Verenigde Staten). Deze laatste zogenaamde volunteer melanoma/skin cancer screenings worden sinds 1985 jaarlijks georganiseerd en worden door de American Academy of Dermatology gesponsord.
Het effect van (volunteer) screening is het grootst wanneer aan bepaalde voorwaarden voor screening wordt voldaan. Het melanoom voldoet aan de meeste van deze principes, het basaalcelcarcinoom en in mindere mate het plaveiselcelcarcinoom doen dit niet. Daarom is de huidige studie alleen gericht op het melanoom van de huid.

In dit hoofdstuk worden bedoelde principes van screening als een vorm van secundaire preventie met betrekking tot huidkanker uiteengezet. Daarnaast wordt het speciale karakter van de beschreven screeningsactie, welke bestaat uit een voorlichtingsprogramma voor het publiek, gevolgd door open dagen, beschreven. Er is hierbij sprake van screening op basis van zelfonderzoek en zelfselectie. In dit kader hebben wij ons zo veel mogelijk beperkt tot het melanoom van de huid. Dit model is zeer aantrekkelijk maar onvoldoende uitgewerkt.

Hoofdstuk 3. De beschreven studie is gebaseerd op gegevens die tijdens de 'Open dagen kwaadaardige moedervlek' op 12 en 19 juni 1993 in Zuid-Limburg zijn verzameld. In dit hoofdstuk worden demografische kenmerken, gegevens over de publiciteitskanalen en beweegredenen van de bezoekers van de open dagen beschreven. In totaal werden de dagen door 4146 personen bezocht. Er waren meer vrouwen dan mannen (respectievelijk 59.5% en 40.5%, $p<0.001$). De meeste bezoekers wilden één of enkele specifieke laesie(s) laten zien (71%). Een minderheid opteerde voor inspectie van de totale huid. Mannen kozen vaker voor een totale huidinspectie dan vrouwen (respectievelijk 29.0% en 21.6%, $p<0.001$). De kranten speelden voor alle groepen de belangrijkste rol in de publiciteitscampagne. Mond-tot-mondreclame en huis-aan-huisbladen kwamen op de tweede en derde plaats. Omdat alleen de lokale radio-en televisiestations op kleine schaal bij de publieksactie waren betrokken, was de impact hiervan te verwaarlozen. "Meer informatie over huidkanker" en "Ik ben bang dat ik huidkanker heb" waren de belangrijkste redenen de open dagen te bezoeken (respectievelijk 27.1% en 26.8%). Opvallend was dat "Zaterdag is een vrije dag" een belangrijke reden was de dagen te bezoeken voor 22.2% van de deelnemers. Van alle participanten bezochten 84.2% de screenings op eigen initiatief. Aanzienlijk meer mannen dan vrouwen waren door een familielid of vriend op de open dagen geattendeerd (respectievelijk 21.6% en 11.9%, $p< 0.001$). Mannen zijn op de open dagen ondervertegenwoordigd en zij zijn minder op de hoogte van de risicofactoren van het melanoom. Dit zijn redenen om toekomstige acties meer op de mannelijke populatie te richten.

Hoofdstuk 4. De uitkomsten van de open dagen in 1990 in Arnhem e.o. (gericht op huidkanker in het algemeen) en in 1993 in Zuid-Limburg (alleen gericht op het melanoom) worden met elkaar vergeleken. Het blijkt dat er een betere selectie plaatsvindt wanneer alleen aandacht aan het melanoom en dysplastische naevi wordt

besteed. Het aantal screenees met klinische verdenking op melanoom nam toe van 1.1% in 1990 naar 1.7% in 1993 ($p=0.04$). Het aantal dysplastische naevi nam toe van 2.1% naar 7.7% ($p<0.001$). Epitheliomen werden minder vaak ontdekt (3.7% in 1990 versus 2.6% in 1993; $p=0.009$). Ook actinische keratosen waren minder talrijk (6.3% versus 1.5%; $p<0.001$). Deze bevindingen zijn uitermate belangrijk met betrekking tot de kosten en effectiviteit van dergelijke campagnes.

Hoofdstuk 5. In de literatuur wordt totale huidinspectie tijdens publieksacties op basis van zelfselectie geadviseerd. Standaard doorgevoerde totale huidinspectie kost relatief veel tijd. Tijdens de Zuidlimburgse actie werd aan 1385 mensen die alleen een bepaald plekje wilden laten zien, gevraagd zich aanvullend van top tot teen te laten nakijken. Het is van belang te vermelden dat bezoekers met atypische naevi of verdenking op melanoom standaard aan een totale huidinspectie werden onderworpen. Er waren 1221 evalueerbare personen. Op deze wijze werden geen extra melanomen ontdekt. Bij histologisch onderzoek konden slechts drie basaalcelcarcinomen worden bevestigd. Omdat totale huidinspectie tijdrovend is en niet meer melanomen blijkt op te leveren, wordt geconcludeerd dat het tijdens screening voor melanoom op basis van zelfselectie niet zinvol is standaard totale huidinspectie uit te voeren. Dit werkt zeker ook kostenbesparend.

Hoofdstuk 6. Of melanoomscreening op basis van zelfselectie zinvol is kan pas worden beoordeeld wanneer de uiteindelijke opbrengst bekend is. Hiervoor is follow-up van de naar de huisarts verwezen bezoekers noodzakelijk. Op deze wijze kan worden nagegaan of er aanvullend pathologisch onderzoek is verricht. In de Zuidlimburgse studie werden 486 bezoekers (11.7%) verwezen wegens voor maligniteit of premaligniteit verdachte afwijkingen (positieve screenees). Personen met "borderline" afwijkingen werden niet verwezen. Verwijzing van "borderline" laesies zou hebben geresulteerd in een aanzienlijke toename van het aantal positieve screenees (18.1%). Ondanks intensieve follow-up kon van 18 personen (3.7%) geen informatie worden verkregen (klinische diagnoses: dysplastische naevi 8, congenitale naevi 9, actinische keratose 1). Bovendien bleken er zeven personen te zijn die afzagen van aanvullend onderzoek en advies (klinische diagnoses: basaalcelcarcinoom 1, dysplastische naevi 5, congenitale naevus 1). De positief voorspellende waarde voor het melanoom was 17.2% en voor de epitheliomen 42.9%. Een adequate follow-up is noodzakelijk en blijkt in Nederland goed haalbaar. Alleen op deze

wijze kan de uiteindelijke opbrengst en het nut van dergelijke campagnes worden bepaald.

Hoofdstuk 7. Per toeval werd tijdens de uitwerking van de resultaten van de screenings ontdekt dat vooral de vroege bezoekers op deze dagen een gemiddeld 'zwaardere' diagnose hadden (meer kwaadaardige huidafwijkingen). Bij nadere analyse werd dit bevestigd. Behalve dat er dus aanwijzingen zijn dat het publiek zich alleszins redelijk kan selecteren, heeft dit ook praktische consequenties en moeten de screening clinics onmiddellijk na de start goed bemand zijn omdat juist dan de meeste verwijzingen plaatsvinden, hetgeen meer tijd kost.

Hoofdstuk 8. In dit afsluitende hoofdstuk worden een aantal eigenschappen van volunteer melanoma screenings nog eens onder de loep genomen. Van belang is dat we hier met een unieke, voor iedereen zichtbare vorm van kanker te maken hebben. Het gegeven dat het hele project binnen de bestaande structuren van onze gezondheidszorg kon worden uitgevoerd, is veelbelovend voor de toekomst. Er kan met de ervaringen van huidige studie onvoldoende worden bepaald of deze opzet kosten-effectief is. Inzicht in de kosten-effectiviteit is wenselijk om besluiten te kunnen nemen over invoering op grotere schaal. Voor het nemen van beslissingen over de ontwikkeling van vervolgstudies is het noodzakelijk dat volunteer melanoma screening op zijn eigen merites wordt beoordeeld. Verwarring met reguliere, bestaande bevolkingsonderzoeken zoals voor het mamma- en cervixscarcinoom is een gevaar. Alleen aanvullend, multidisciplinair onderzoek zal uiteindelijk kunnen bepalen of deze benadering kosten-effectief is en een zinvolle bijdrage levert om de aanzienlijke morbiditeit en mortaliteit van het melanoom van de huid te bestrijden. Tot slot wordt een draaiboek gepresenteerd voor een regionale of landelijke screeningsactie (appendix).

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CURRICULUM VITAE

Michette de Rooij werd geboren op 19 september 1963 te Zeddam (gem. Bergh Gld). In 1981 behaalde zij het diploma Gymnasium B aan het dr. Mollercollege te Waalwijk. Van 1981 tot 1987 studeerde zij geneeskunde aan de Rijksuniversiteit Limburg te Maastricht (thans Universiteit Maastricht). Tijdens haar studie was zij als student assistent werkzaam in het Skills-lab van de faculteit geneeskunde (hoofd: dr. P.M.T.A. Bartholomeus). Tevens was zij tijdens haar studie bestuurslid van studentenvereniging KOKO. Direct na het behalen van het basisartsdiploma in november 1987 startte zij als assistent-geneeskundige Interne Geneeskunde in het azM te Maastricht (hoofd: prof.dr. J.A. Flendrig†). In november 1988 werd begonnen als assistent-geneeskundige op de afdeling Longziekten van het azM te Maastricht (hoofd: prof.dr. L.H. Greve†). Vanaf juni 1989 was zij werkzaam als assistent-geneeskundige in het De Weverziekenhuis te Heerlen (dr. J. Wuite, dr. M.J.T. Go en drs. J.C.C.A. Lambers). Op 1 november 1990 werd gestart met de opleiding Dermatologie in het azM te Maastricht (opleiders: prof.dr. W.J.B.M. van der Staak, prof.dr. H.A.M. Neumann). Tijdens haar opleiding startte zij met wetenschappelijk onderzoek. Op 1 augustus 1994 werd zij geregistreerd als dermato-venereoloog. Sinds 1 september 1994 is zij als universitair docent verbonden aan de afdeling Dermatologie van het Academisch Ziekenhuis St Radboud te Nijmegen met als aandachtsgebieden flebologie, dermatochirurgie/oncologie (hoofd: prof.dr.dr. P.C.M. van de Kerkhof). Het onderzoek werd hier voortgezet en afgerond.

LIST OF ABBREVIATIONS

AAD	:	American Academy of Dermatology
ABCD(E) rule	:	mnemonic for: Asymmetry, Border irregularity, Colour variegation, Diameter >6mm, and Elevation
AJCC	:	American Joint Committee on Cancer
ALM	:	acral-lentiginous melanoma
DNS	:	dysplastic naevus syndrome
DTIC	:	dacarbazine
LM	:	lentigo maligna
LMM	:	lentigo maligna melanoma
NM	:	nodular melanoma
PUVA	:	photochemotherapy
SSM	:	superficial spreading melanoma
UICC	:	Union Internationale contre le Cancer
UV	:	ultra violet
WHO	:	World Health Organization